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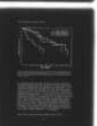
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**HEMATOLOGY-ONCOLOGY SYMPOSIUM  
PRESENT CONCEPTS IN INTERNAL MEDICINE**

LTC Glen R. Justice, MC, LTC Melvin L. Butler, MC, Nina Z. Sanders, B.A., and  
Cathleen E. Swee, M.A.

Letterman Army Medical Center  
Presidio of San Francisco, CA 94129

1977-1978

Hematology-Oncology Symposium

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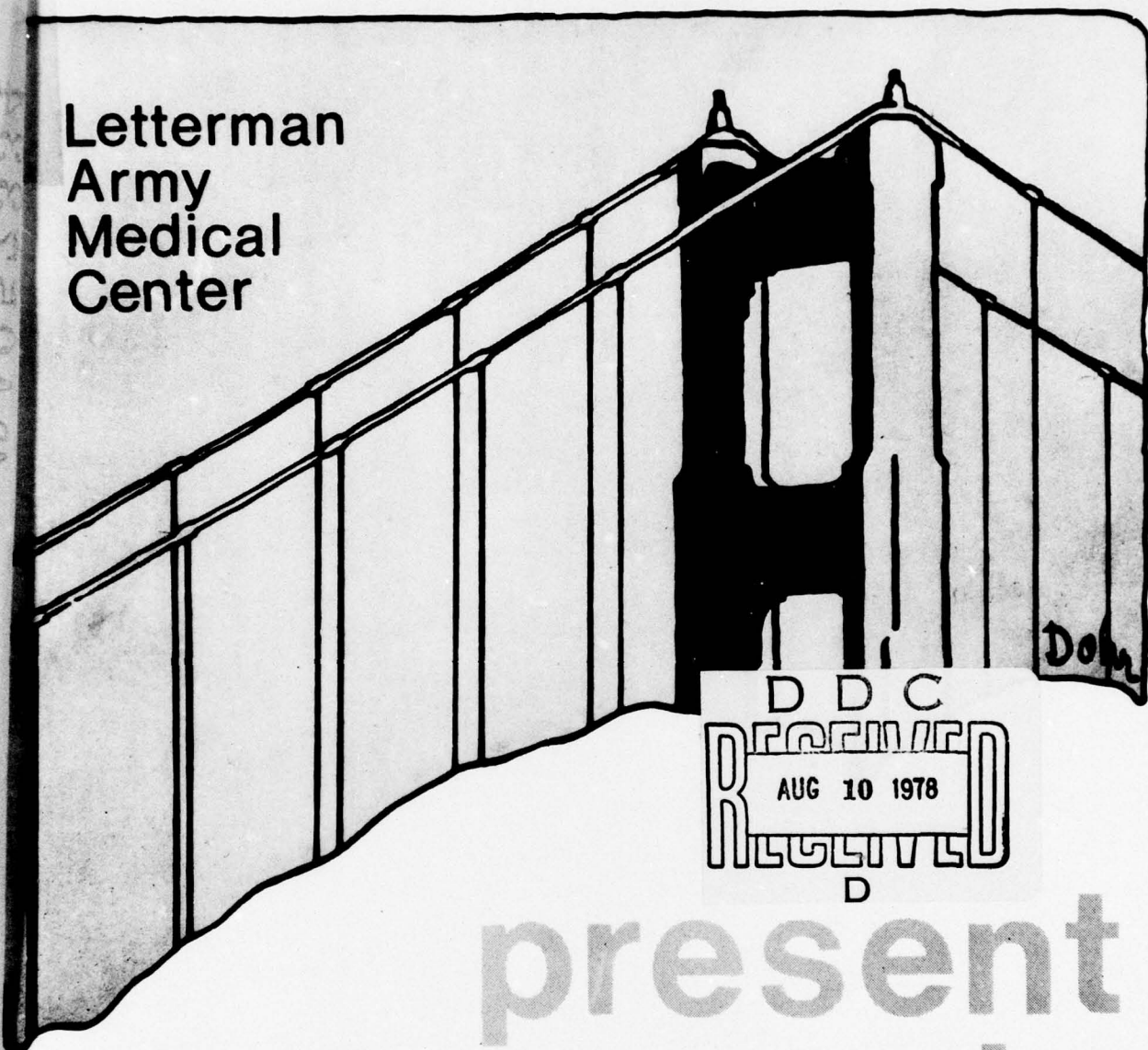
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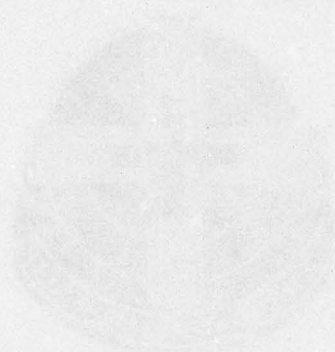
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## PRESENT CONCEPTS IN INTERNAL MEDICINE

*Hematology-Oncology Symposium, Winter 1977-1978*

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In keeping with past issues this quarter's edition of *Present Concepts* takes the form of a symposium written by our Hematology-Oncology Service. In the future our format may vary with articles from various subspecialties combined in one issue. We invite individuals in the health sciences in other military medical facilities to submit material for consideration for publication in *Present Concepts*. Appearance in our journal does not preclude later publication of the same article in a national journal.

Manuscripts should be sent to the editor, LTC Melvin L. Butler, MC, Box 446, Letterman Army Medical Center, Presidio of San Francisco, California 94129.

## FOREWORD

Each topic selected for this Hematology-Oncology Symposium was required to meet the following two criteria: it must have clinical relevance, and it must have undergone an "explosion" in terms of new information and understanding.

The first article, "General Concepts of Chemotherapy," is aimed at the level of the house staff physician and internist, and gives a detailed approach to treating the cancer patient with chemotherapy. It is meant to be highly practical and to aid the non-oncologist physician in treating oncology patients.

Granulocyte transfusion in the neutropenic patient has been a highly controversial field, but, with the increasing accumulation of data, it is becoming more the "state of the art." Dr. Congdon, who directs Letterman's large granulocyte transfusion unit, has done an excellent job in reviewing this complex field in his article, "Granulocyte Transfusion Therapy."

The next two articles, "Hodgkin's Disease — Current Concepts," and "The Non-Hodgkin's Lymphomas: A Summary," by Drs. Gandara and DeGreen, respectively, deal with an area that has undergone tremendous growth and development in the last ten years. The breakthroughs that have occurred in treating these diseases in the last decade are second to none in medicine.

The last article is a superlative and detailed review by Dr. Dabe on the complicated area of "Quantitative Platelet Disorders."

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Guest Editor

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## GENERAL CONCEPTS OF CHEMOTHERAPY

LTC Glen R. Justice, MC

### The Cancer Problem

This year, cancer will be the second leading cause of death in the United States. More precisely, over 400,000 people, including 33,000 women with breast cancer, will die of cancer this year, and more than 100,000 breast cancers will be diagnosed. Another way of viewing it is that seven of every hundred women in the United States will develop the disease at some point in their lives.

From a macromolecular level, all living organisms have an inherent capacity to multiply and divide. This mitotic process is usually highly precise and organized. Cells cease to divide for a number of reasons. In man, this is reflected by the healing of a cut finger; in cell culture, normal human cells stop dividing after 20 to 30 divisions. This is not true of neoplastic cells, where uncontrolled proliferation is the norm. In cell culture, normal cells seem to achieve control by an unknown feedback mechanism probably resulting from cell contact inhibition phenomenon. In cancer, cells fail to stop multiplying when they reach a critical mass and the uncontrolled growth leads to death of the organism. Clinically, the major hallmarks of neoplasia are (1) local spread, invasion, and destruction, and (2) lymphatic and hematogenous spread to other organs of the body or metastasis to bone, liver, lung, and other parts of the body.

### Treatment of Cancer

Kinetic studies of leukemia in animals and humans and of other human cancers show that the disease is usually only clinically appreciated at  $10^9$  cells and death usually ensues by  $10^{12}$  cells. In the treatment of cancer, a basic, yet fundamental assumption is that all malignant cells should be destroyed or eliminated. The critical concept of "killing the last cancer cell" is the very cornerstone of modern oncology. In the past, usually only one mode of therapy was used, but the very foundation of modern oncology is the principle of multimodality approach to cancer therapy. Specifically, one

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uses a combination of surgery, radiation therapy, chemotherapy, and immunotherapy where applicable. In this paper, I will deal primarily with chemotherapy, although many of the clinical principles apply to other modalities as well.

*Historical Perspectives of Cancer Chemotherapy*

Modern cancer chemotherapy had its genesis in the medical research of World War II. A class of compounds, the nitrogen mustards, were developed in a search for more effective vesicant war gases. After several people had been accidentally exposed to the nitrogen mustard chemicals, it became apparent that they also caused systemic effects, nausea, vomiting, and alopecia, but of even greater importance, bone marrow depression or neutropenia. Several investigators recognized that these systemic effects might also reduce the number of malignant cells in certain cancers, especially those affecting bone marrow and the lymphatic system, leukemias, and lymphomas. By 1946, more than 150 patients had been treated, and definite responses were seen in Hodgkin's disease and non-Hodgkin's lymphoma. At the same time, another critical breakthrough was taking place. Scientists engaged in research on nutrition and vitamin structure found that slight modification of a vitamin structure not only inactivated that vitamin or key enzymes required for its synthesis, but also acted as a metabolic antagonist. Often these vitamins were critical for the synthesis of DNA, RNA, and other vital proteins. A new class of growth-arresting drugs, the antimetabolites, evolved. The discovery of folic acid in 1946 was important to the development of anticancer drugs. This B vitamin was found to be essential for normal blood formation. Doctor Sidney Farber made the astute clinical observation that giving folic acid to children with acute lymphocytic leukemia accelerated their leukemia. In 1948, Doctor Farber demonstrated that aminopterin, an antimetabolic of folic acid, produced dramatic and complete remissions in children acutely ill with leukemia; unfortunately, although these remissions were impressive, they were short-lived. The advances in medical research provided by military programs, and the ingenious research by Doctor Farber provided great impetus to the development of oncology and chemotherapy.

## *General Concepts of Chemotherapy - Justice*

### Criteria for Established Chemotherapy

In contemplating treatment of the cancer patient, the clinician must consider several critical concepts. The first of these concepts is the degree to which a tumor is treatable; if one is to "buy into" the toxicity of chemotherapy, one must consider the potential therapeutic advantage to the patient. In accessing the risk/reward ratio, one must have some appreciation for the probability of cure or improvement.

Most human cancers can be classified into one of four categories: (1) tumors potentially curable; (2) increased survival; (3) palliation; and (4) experimental therapy (no proven increased survival in the majority of patients so treated). See Table.

TABLE  
ADVANCED TUMORS TREATED SOLELY WITH CHEMOTHERAPY

Tumor Potentially Curable	Increased Survival	Palliation	Experimental - Minimal Benefit
1. Choriocarcinoma	1. Testicular cancer	1. Colon cancer	1. Cervical cancer
2. Burkitt's lymphoma	2. Non-Hodgkin's lymphoma	2. Chronic adult leukemias	2. Pancreas cancer
3. Acute lymphocytic leukemia	3. Breast cancer	3. Prostate cancer	3. Lung cancer
4. Hodgkin's disease	4. Adult acute leukemias		4. Malignant melanoma
5. Several childhood malignancies	5. Multiple myeloma		
	6. Oat cell carcinoma of the lung		
	7. Ovarian carcinoma		

Second, one must have a healthy appreciation of the potential toxicity of chemotherapy. Most chemotherapeutic agents affect the cells that have the most rapid turnover time in the body: bone marrow, hair follicles, and gut endothelium, hence, the common side effects of pancytopenias, alopecia, mouth sores, diarrhea, mucositis, and gastrointestinal

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bleeding. Any physician poised to treat the cancer patient with chemotherapeutic drugs must make a rapid assessment of these organ systems if severe toxicity and potential drug-induced mortality are to be avoided. In regard to the hematopoietic system, it is vital to check the complete blood count and the platelet count. Bodey et al directly correlated severe life-threatening sepsis with absolute granulocyte counts below  $1,000/\text{mm}^3$  and specifically below  $500/\text{mm}^3$ . Consequently, one would like to see an *absolute* granulocyte count above 2,000 before treating with chemotherapy. This rule obviously does not apply if the anticancer agent does not affect bone marrow, or if the patient's low white blood cell count is secondary to bone marrow replacement by tumor as in acute leukemia or certain lymphomas. In regard to platelets, one seldom encounters significant bleeding if platelet counts are above  $50,000/\text{mm}^3$ ; thus, one would usually not treat with a chemotherapeutic agent unless the platelet count exceeds  $100,000/\text{mm}^3$ . The physician should realize that platelet counts may be inaccurate and should doublecheck the platelet count by looking at the peripheral smear with a visual estimate of the platelets.

Gastrointestinal toxicity can best be assessed by a thorough check for melena, diarrhea, mouth sores, or hematochezia, and by a careful oral examination for stomatitis, mouth ulcers, or mucositis. The oral mucosa is a good index of what is happening throughout the entire enteric system; consequently, one would usually not treat with chemotherapy the patient with moderate stomatitis, mucositis, mouth sores, impressive diarrhea, or new gastrointestinal complaints.

A third clinical concept is an appreciation for the specific toxicities that are related to specific chemotherapeutic agents, e.g., cardiomyopathy associated with adriamycin, hemorrhagic cystitis of Cytosan®, pulmonary fibrosis associated with bleomycin, and peripheral neuropathies related to vincristine. This area is obviously complicated and extensive but vital for the patient. For example, when using Cytosan, the life-threatening complication of hemorrhagic cystitis can be avoided if one ensures excellent hydration of the patient. Mortality secondary to adriamycin cardiomyopathy can be reduced to about 1% if one does a careful cardiac examination and serial electrocardiograms and keeps the total dose below  $550 \text{ mg}/\text{m}^2$  ( $450 \text{ mg}/\text{m}^2$  if previous



mediastinal radiation therapy). Before giving vincristine, one should check the patient's motor strength by having him walk on his heels, and find out if the patient is experiencing severe foot drop or paresthesias, symptoms which would contraindicate the use of this drug.

A fourth clinical concept in using chemotherapy is to have some knowledge about how the drug is metabolized and excreted. For example, Cytosan and methotrexate are predominantly renally excreted; a healthy appreciation of renal function as reflected in blood urea nitrogen (BUN), creatinine, and creatinine clearance are, therefore, important in adjusting downward the dose or even holding therapy if severe renal impairment exists. Adriamycin is primarily excreted through the biliary apparatus; a careful check of bilirubin and liver function tests is important. As a general principle, the chemotherapist should always obtain BUN, creatinine, bilirubin, and liver function tests and know the mode of excretion of the drug before administering it.

The last clinical concept, and in the author's opinion the most important one, is the idea of measurable tumor parameters. When one institutes potentially life-saving or palliating chemotherapy with its frequent association with toxicity, one needs to know if the tumor is shrinking, being held stable, or advancing. There is nothing more tragic than the cancer patient treated with toxic agents whose tumor is progressing in spite of the medication. In this setting, clinical management is compromised in two ways: (1) toxicity with no efficacy, and (2) potential delay in other more effective therapy.

Consequently, before embarking on a trial of chemotherapy, one should have as many measurable or quantifiable criteria as possible to scientifically evaluate the response to therapy. Beta human chorionic gonadotropin (HCG) subunits in choriocarcinoma or testicular cancer, serial measurements of paraprotein by serum protein electrophoresis in multiple myeloma, and measurements of lymph node size by physical examination or chest nodules by serial chest x-rays are examples. The use of lymphangiograms, x-rays, computerized axial tomography (CAT) scans, liver, bone, and gallium scans as well as careful physical examination with specific tumor measurements can also be helpful.

## CELL KINETICS

### The Cell Cycle

In order to understand the effects of chemotherapeutic agents on both normal cells and neoplastic cells, it is important to understand mitosis and the cell cycle. The concept of drug activity during only a phase of the life cycle of proliferating malignant cells has become increasingly important to both the theoretical and the practical aspects of cancer therapy design. Mitosis occupies a discrete phase of the life cycle (Figure 1).

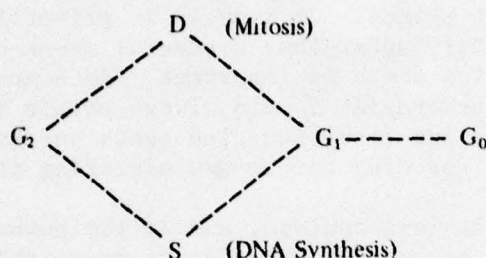


Figure 1. Cell cycle.

The  $G_1$  phase for a long time was considered to be a relatively quiescent period, but this is not the case. In general, replicating cells are most sensitive to attack by commonly used antimetabolites during S phase (the DNA synthesis phase). It is probable that the  $G_2$  phase is the point of cellular life cycle at which certain mitotic inhibitors such as vincristine and bleomycin exert their effects. The D phase is when the cell actually undergoes mitosis. Agents that are mainly effective during a particular phase of the cell cycle such as cellular DNA synthesis are labeled "cell cycle specific" or "phase specific" drugs. Those agents whose action is prolonged or predominantly independent of DNA synthesis are called "cell cycle nonspecific" or "phase non-specific" drugs.

### Gompertzian Growth Curve

Normal and neoplastic cells may be influenced by certain growth factors; both appear to divide rapidly when the cell population is small, and to grow and multiply more

slowly when it is large. Early growth is clearly exponential with a high growth fraction and short doubling time (Figure 2).

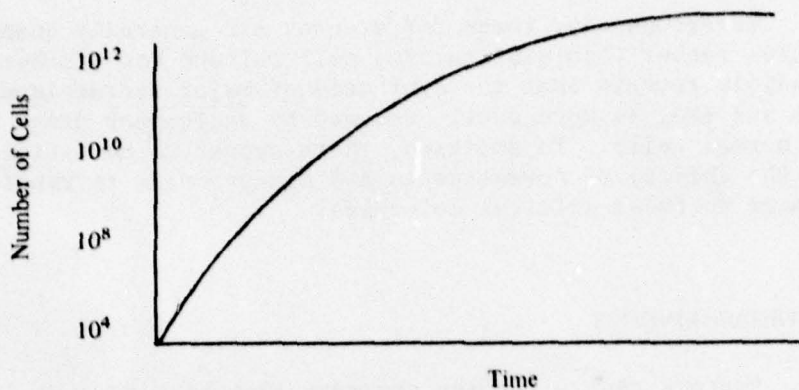


Figure 2. Gompertzian growth curve.

As time passes, the doubling time increases, and the growth rate decreases. At least 19 different animal tumors and human acute leukemia and multiple myeloma conform to the gompertzian pattern of growth. A major clinical implication of the mathematical growth concept is that the choice of chemotherapeutic drugs should probably be different for large (slowly growing) tumors than for small (rapidly proliferating) tumors. When the tumor is small and growing rapidly, a high proportion of cells are in S phase or DNA synthesis. At this point, one should logically use a cell cycle specific agent effective against rapidly dividing cells. In contrast, an advanced tumor with a low growth fraction and a slow increase in size may respond more effectively to a phase nonspecific drug.

#### Factors Affecting the Usefulness of Drugs

In considering the mechanism of the action of chemotherapeutic drugs, one must consider the concept and desirability of a selective biologic edge. For example, penicillin interferes with cell wall synthesis and, since bacteria have cell walls and mammalian cells do not, penicillin selectively kills the bacteria. Except for the drug L'asparaginase, this type of selective biologic edge is exceedingly rare in antineoplastic agents. Clinically



useful anticancer drugs in general have a greater toxicity for malignant than for normal cells. Selective toxicity exploits a difference between malignant and normal cells.

Unfortunately, these differences are generally quantitative rather than qualitative; cell culture and biochemical analysis reveals that the synthesis of major macromolecules, DNA and RNA, is more easily damaged by anticancer drugs than in normal cells. In addition, there appear to be differences in the ability of normal cells and cancer cells to repair damage to these critical molecules.

#### PHARMACOKINETICS

Factors that alter the concentration of a drug at its site of action or the period of time during which the drug is available for activity at the biologic receptor must be considered in the use of anticancer drugs. The critical concept of drug efficacy of anticancer agents is often the relationship between drug concentration and time. Factors affecting this relationship are as follows:

1. *Drug absorption.* Route of administration is by mouth, intravenous, intramuscular, intra-arterial, etc. An example is the erratic absorption of 5-fluorouracil (5-FU) orally as compared to intravenous administration. The importance of route of delivery is reflected in the higher response rates in cancer of the colon treated with intravenous rather than oral 5-FU.

2. *Distribution.* In some instances, drugs may accumulate in certain areas as a result of binding to plasma proteins, active transport, or high solubility in fat. The converse of this is that some drugs may be excluded from certain areas because of the influence of these drugs on distribution. This phenomenon is referred to as the sanctuary effect. The brain, where tumor cells appear to be inaccessible to most anticancer drugs because of the blood brain barrier, is an example of such a sanctuary.

3. *Biotransformation.* An example is Cytosan; this drug is inactive until it is metabolized in the liver where it becomes an active drug.



4. *Excretion.* Methotrexate and Cytosin are examples of drugs predominantly excreted by the kidneys, whereas adriamycin and vincristine are excreted primarily by the biliary tract.

5. *Drug - drug interactions.* The whole pharmacologic area of drug - drug interaction is an exciting but embryonic area. For example, the drug methotrexate is primarily transported in the serum bound to albumin, and both aspirin and sulfa drugs are known to displace methotrexate and thereby increase free drug levels and drug toxicity. Allopurinol, a xanthine oxidase inhibitor, affects the metabolism of 6-mercaptopurine. Mercaptopurine is metabolized by xanthine oxidase and one must, therefore, decrease the dose of mercaptopurine when using it with allopurinol.

6. *Drug schedules and combination chemotherapy.* Studies with experimental animal tumors have conclusively demonstrated the critical importance of drug scheduling in therapy. An antimetabolite that kills cells predominantly in S phase, ARA-C, must be given frequently in order to insure contact with cancer cells during this vulnerable period. When the drug is given frequently in low dose (maximum exposure to cancer cells in S phase), it is possible to cure some forms of mouse leukemia, whereas maximally tolerated doses of the drug administered at less frequent intervals fail to prolong survival. On the other hand, Cytosin, a non-cell cycle specific agent, achieves optimal suppression when given on a high dose, intermittent schedule. In general, a solid tumor with a large tumor mass grows slowly, has a small growth fraction, and a prolonged tumor volume doubling time. Because relatively few of its cells are dividing, this tumor is generally insensitive to phase-specific drugs. Thus, the usual treatment for advanced non-hematologic tumors has been with phase nonspecific drugs, such as alkylating agents. Successful treatment with such phase nonspecific drugs may render the tumor more susceptible to phase-specific drugs by converting the tumor from one with a low growth fraction and a few cells in S phase to one with a high growth fraction (gompertzian curve) and many cells in S phase. This concept is supported by hamster plasmacytoma which is cured by first treating with the cell nonspecific alkylator Cytosin, then the phase specific drug ARA-C, and not vice versa.

#### IMMUNOSUPPRESSION RELATED TO CHEMOTHERAPY

The immunologic factors studied with chemotherapy include macrophage entry into experimental inflammatory sites (skin windows), response of antibodies to antigen challenge, and lymphocyte blastogenic transformation to phytohemagglutinin. With bolus or pulse chemotherapy there is a profound decrease in all these parameters during therapy. Within two or three days, however, there is a complete recovery of immunologic response. This depression is much more prolonged with daily chemotherapy (as opposed to pulse). Thus, when chemotherapy is given intermittently, the patient's immunologic function is normal most of the time. It is important to note that an intermittent intensive course of chemotherapy appears to suppress cellular immunity less than does continuous low dose chemotherapy. This has obvious theoretical implications in regard to patient therapy.

In summary, the treatment of cancer may seem extremely mystical and complex, but this is not usually the case. Rather, modern oncology consists of applying sound principles of pharmacology, clinical medicine, common sense, and a multimodality approach in an effort to continue to improve the plight of the cancer patient. Through this philosophy, modern oncology is now curing some tumors that were uniformly fatal, and is extending survival and increasing the quality of life in many other cancer patients. What is so exciting is that "we have only just begun."

*General Concepts of Chemotherapy - Justice*

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## GRANULOCYTE TRANSFUSION THERAPY

LCDR James E. Congdon, MC

### Introduction

The current management of most malignant diseases today includes the use of radiation and/or chemotherapy. The major toxicity in either case is suppression of bone marrow locally from radiation therapy or generalized from chemotherapy.

In the late 1950s, the major cause of death in patients with leukemia was bleeding, with infection a distant second. Since the advent of effective platelet transfusions in the past 10 years, the incidence of deaths related to hemorrhage has drastically decreased. A retrospective analysis at the National Cancer Institute from 1965 to 1971 shows that infection accounted for 69% of deaths in patients with acute leukemia and hemorrhage accounted for only 11% of deaths. /1/ Thus, the increasingly aggressive use of chemotherapy and radiation therapy made it crucial to devise a method for treating infectious complications during periods of myelosuppression.

### Granulocyte Kinetics

Table 1, based on data from Cartwright et al /2/, illustrates the total body distribution of granulocytes as determined by  $DF^{32}P$  labeling in normal volunteers. A man weighing 70 kg is estimated to harbor approximately  $140 \times 10^{10}$  granulocytes. Of this number, approximately  $130 \times 10^{10}$  or 96.4% of the cells are estimated to reside in the bone marrow pool. The remaining 3.6% comprise the total blood pool evenly divided between circulating granulocytes and marginated cells. These compartments are freely interchangeable.

One of the first things to consider when discussing granulocyte transfusion therapy is the relationship between the circulating granulocyte level and the risk of infection to the patient. Bodey et al /3/ demonstrated that the risk of infection was inversely related to the circulating granulocyte pool and that the risk became clinically significant when the circulating granulocyte concentration dropped below 1,500 polymorphonuclear cells (PMN) per ml of blood. The

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risk continued to escalate, reaching a maximum risk of susceptibility to infection when the circulating PMN count dropped below  $500/\text{mm}^3$ . This risk applied both to the frequency and to the severity of the individual infection encountered in the patient. Although sterile protected environments combined with new and powerful antibiotics have significantly enhanced survival in septic neutropenic patients, they are not the final solution. Table 2 demonstrates that with use of even the most efficacious new and powerful antibiotics, we can expect a short-term patient survival of no more than 55%. /4,5,6,7/

TABLE 1  
NORMAL GRANULOCYTE DISTRIBUTION

Site	Number of cells ( $\times 10^9/\text{kg}$ )	Total cells for 70 kg man ( $\times 10^{10}$ )	Fraction of total body PMNs* (%)
Total blood PMN pool	0.70	4.9	3.6
Circulating PMN pool	0.31	2.2	1.7
Marginal PMN pool	0.39	2.7	1.9
Total bone marrow PMN pool	18.60	130.0	96.4

\* PMN = polymorpho-nucleated granulocyte

TABLE 2  
NATURAL HISTORY OF INFECTION  
IN NEUTROPENIC CANCER PATIENTS (1972-1975)

Study	PMN* level/ $\text{mm}^3$	Overall Success (%)	Success % blood count and patients	Antibiotics
Greene et al	< 1,500	71	57	CAR-GEN-CEP
Middleman et al	< 1,000	61	56	CAR-CEP versus CAR-KAN
Tattersall et al	< 1,000	75	54	Four or five selected antibiotics
Klastersky et al	< 500	42	30	CAR-CEP versus CAR-CEP-GEN

\* PMN = polymorphonuclear cells



#### Granulocyte Collection

Because whole blood contains a relatively small number of granulocytes, it is impractical to collect PMNs from normal donors by ordinary phlebotomy or other routine methods. Granulocyte transfusions in humans were first conducted in the early 1960s by means of a single unit phlebotomy, using donors with chronic myelogenous leukemia (CML). /8,9/ These donors provided a ready source of a large number of mature, apparently normal, granulocytes as well as a population of blast cells. Inherent disadvantages such as the propriety of infusing blast cells, limited availability of CML donors, poor post-transfusion increments and occasional occurrence of graft versus host disease in the recipient, soon became apparent. Although CML donors are no longer used, many of the principles learned from these trials have set the foundation for the kinetics of modern granulocyte transfusion therapy.

In 1961, Morse /8/ reported that he obtained the best clinical results when the number of granulocytes transfused approached  $1 \times 10^{11}$  and that he saw little or no clinical effect when the number of granulocytes transfused was fewer than  $1 \times 10^9$ . Buckner et al /9/ also noted that generally they saw little increment in the recipient's white blood cell count following transfusion even when an adequate number of granulocytes were infused to give beneficial clinical results. These workers postulated that the apparently effective granulocytes immediately migrated to the site of infection. This idea was confirmed by Morse /8/, using PMNs tagged with CR<sup>51</sup> and monitoring these accumulations in areas of inflammation. Less than 20% of the tagged PMNs could be recovered one hour after transfusion, even in those patients who seemed to derive clinical benefit from transfusion.

In 1965 Freireich et al /10/ published results of their development of continuous flow centrifugation (CFC) in a joint venture between the National Cancer Institute and the International Business Machine Corporation (IBM). /11/ The procedure allows for a large volume of blood to be processed continuously through a centrifuge bowl with minimal loss of components to the donor other than PMNs. Instrumentation is now available through IBM, Aminco, and Hemanitics Corporations. The efficiency of leukocyte removal on an individual pass through the machine of a unit of blood is approximately 25%

of the PMNs. A large volume of blood must, therefore, be processed in order to achieve  $1 \times 10^{10}$  granulocytes, i.e., an effective number of granulocytes to achieve clinical results. Approximately 7 to 10 liters of the donor's blood are processed per donation at a continuous flow rate of approximately 40 ml per minute. The CFC technique yields between .2 and  $.79 \times 10^{10}$  granulocytes collected from unstimulated donors. Various workers have reported effective stimulation of donor granulocytes to increase yields with such agents as steroids, etiocholanolone, hydroxyethyl starch, and endotoxin. /11,12,13/ Many of these agents pose serious ethical questions as to their use in healthy volunteer donors. Etiocholanolone and endotoxin induce fever and pain at the injection site in the donor; hydroxyethyl starch is a potent intravascular volume expander and causes fluid retention in older donors. There is much controversy over the use of glucocorticoids as an agent in donors to increase granulocyte yields. Several articles published recently, however, point out their safety and utility. These glucocorticoids have probably become the agent of choice for use in stimulating increased PMN yields in donors. /14,15,16/

In 1966, McKenna /17/ reported on the use of granulocyte adhesion to nylon fibers as a method of preparing granulocyte poor blood. In 1971, Djerassi /18/ reported that granulocytes bound to nylon fibers can be released if washed with ACD solution, thereby selectively trapping granulocytes and collecting them in a concentrated solution. This system, known as filtration leukapheresis (FL), has been developed commercially for general use by the Fenwal Corporation. Unstimulated collections average approximately  $1.4 \times 10^{10}$  cells with the passage of 4 to 5 liters of blood. Yields from donors stimulated with steroids are somewhat higher, averaging 2 to  $3 \times 10^{10}$  cells. Table 3 shows the average yield at Letterman Army Medical Center (LAMC) using these two common PMN collection techniques.

Another system, developed by the Hemanitics Corporation, is similar in principle to the CFC system except that it operates by intermittent flow centrifugation using ACD and hydroxyethyl starch to complex out the red blood cells. Huestis /19/ reports yields averaging  $1.4 \times 10^{10}$  granulocytes after collection periods of two and one half hours.

TABLE 3  
NEUTROPHIL COLLECTION AND DONOR REACTION DATA

Technique	Mean Neutrophil Collection Per Run $\times 10^9$		Incidence of Donor Reactions by Technique	
	Stimulated	Unstimulated	Stimulated	Unstimulated
CFC*	9.4 (151) <sup>†</sup>	8.2 (106) <sup>†</sup>	6.6% (10/151) <sup>†</sup>	6.6% (7/106) <sup>†</sup>
FL ‡	19.2 (294) <sup>†</sup>	16.8 ( 77)*	4.8% (14/299) <sup>†</sup>	9.1 % (7/ 77) <sup>†</sup>

\* CFC = continuous flow centrifugation

<sup>†</sup> ( ) = number of runs

‡ FL = filtration leukapheresis

#### In Vitro Granulocyte Transfusion Function

Many reports have been published in the last several years on the various aspects of relative and absolute granulocyte function using CFC and FL collection systems. In this paper, I will attempt to outline only those that have direct bearing on their clinical effectiveness. McCullough /20/ observed that with CFC collected cells, 3% had increased vacuolization and 8% were unrecognizable by routine light microscopy; in contrast, 23% of FL granulocytes had increased vacuolization and 13% were unrecognizable. He next tried to correlate the morphologic changes with changes in *in vitro* function testing. Using various *in vitro* tests (staphylococcal strain 502 killing assay, granulocyte chemotaxis) and intermediary metabolism tests including the nitro-blue tetrazoleum test and the oxygen consumption assay, McCullough /20/ showed that CFC granulocyte activity was equal to controlled granulocytes collected from normal donors by sedimentation. Filtration leukapheresis PMNs, on the other hand, demonstrated a consistently decreased bacteriocidal killing ability averaging 64% of bacteria killed at two hours, compared to 87% for CFC PMNs and sedimented control PMNs. Both CFC and FL cells had normal *in vitro* function to chemotaxis assay, quantitative NBT test, and  $O_2$  consumption assay (Table 4). /20/

Klock and Bainton /21/ have demonstrated that after incubating with nylon fibers, FL granulocytes consistently contained less acid phosphatase and beta-glucuronidase than did control PMNs, and that incubated PMNs harbored decreased



numbers of cytoplasmic granules and had increased vacuolization. These authors surmised that FL granulocytes entered into variable degrees of irreversible membrane damage that accounts for a decrease of their *in vitro* functions.

TABLE 4  
IN-VITRO GRANULOCYTE FUNCTION STUDIES

	Bactericidal assay % killing at 2 hrs		Chemotaxis assay (Number of cells/10 hpf)		NBT assay $\Delta$ OD		O <sub>2</sub> consumption micro-l/hr	
	CFC	FL	CFC	FL	CFC	FL	CFC	FL
Before donation	87	76	191	172	...	0.124	...	...
PMN concentration	87	64	222	179	0.114	0.142	8.37	10.11
After donation	85	80	183	173	...	0.129	...	...
CPD control	86	81	187	167	0.113	0.123	6.95	8.65

Abbreviations: hpf = high power field; NBT = nitroblue tetrazolium dye test; OD = optical density; CFC = continuous flow centrifugation; FL = filtration leukapheresis; PMN = polymorphonuclear cells; CPD = citrate phosphate dextrose

In a second paper, McCullough /22/ confirmed the impressions of Klock and Bainton /21/ by demonstrating that the FL granulocytes that adhered most tenaciously to the nylon fibers had the poorest staphylococcal killing ability. That is, those PMNs that easily eluted with a first ACD wash demonstrated 83% killing ability, whereas only 63.9% and 61% killing abilities were seen in cells collected by second and third ACD elutions.

Wright /23/ showed that by decreasing the time of exposure of the PMN to the nylon fiber, one could increase the *in vitro* function of the cell collected and that pretreating the donor with steroids increased not only the PMN yield but the quality of the FL granulocyte as well. He surmised that the quality of the steroid-treated cell was improved because the steroid caused it to bind less tenaciously to the nylon fiber.

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There has been much controversy in the literature in the last several years as to whether pretreatment of donors with steroids to increase granulocyte yield results clinically in a qualitatively and functionally inferior product. Several recent studies, however, point to the potential efficacy of this form of donor pretreatment. /14,15,16/ Shoji and Vogler /14/ noted a statistically significant increment in the number of neutrophils collected from donors pretreated with 120 mg/M<sup>2</sup> of hydrocortisone over those collected from non pretreated donors. They found that granulocytes from each group were equally effective in the phagocytosis of yeast particles and *in vitro* bactericidal activity.

Higby et al /16/ administered dexamethasone to 51 PMN donors and withheld it from 52 control donors undergoing FL transfusions. They found statistically significant advantages in the steroid-treated donors in all areas investigated, including an increase in PMN yield, increase in post-transfusion increment in recipients, and a decrease in the incidence of donor and patient reactions. They postulate that steroids increase donor PMN yields by increasing peripheral vascular demargination, that improved morphology is the result of steroid inhibition of complement activation at the nylon fiber, and that the low rate of donor and recipient reactions is due to steroid stabilization of the granulocyte lysosomal membrane. Finally, Glasser et al /15/ noted similar results in 28 donors pretreated with 4 mg of dexamethasone prior to PMN collection as compared to matched controls. They concluded that the functional competence of PMNs used for granulocyte transfusion therapy is not altered after short-term exposure to steroid treatment.

To summarize the *in vitro* data of CFC versus FL collection: (1) CFC cells yield slightly lower numbers of morphologically normal cells; (2) *in vitro* testing reveals them to be similar to normal granulocytes; and (3) *in vivo* survival time approximates controlled sediment cells. Recipient reactions are rare, and functionally effective platelets as well as PMNs are transfused. Disadvantages of using CFC cells include greater expense with increased technician time and increased donation time (four hours versus two hours with the FL technique). Filtration leukapheresis cells, on the other hand, yield a slightly higher number of PMNs with a slight decrease in *in vitro* bacteriocidal killing ability. A slight

increase in both donor and patient reactions with this technique has been noted (Table 3). The FL technique is less expensive, requires only two hours' donation time, and can be accomplished with a minimum of technical equipment. The use of glucocorticoids appears to be safe and effective for increasing donor PMN yields and may be of particular significance for use in FL donations. Steroids are thought to yield a larger number of functionally superior cells because they decrease the severity of membrane damage resulting from PMN adherence to the nylon fibers.

#### Criteria for Support

To be eligible to receive neutrophil support at LAMC, the patient must fulfill the following three criteria: (1) absolute neutropenia, as defined by a circulating PMN count fewer than  $500/\text{cm}^3$ ; (2) clinical sepsis as evidenced by fever greater than  $38.3^\circ\text{C}$ ; and (3) continued fever after 24 hours of adequate antibiotic coverage. We define adequate antibiotic coverage as triple therapy consisting of a cephalosporin,  $4\text{ gm}/\text{M}^2$  per day in divided doses, carbenicillin  $20\text{ gm}/\text{M}^2$  per day in divided doses, and gentamycin  $5\text{ mg}/\text{Kg}$  per day in divided doses, renal function permitting. Blood cultures need not be positive at the time PMN transfusions are instituted, but should have been drawn prior to the start of antibiotic therapy. Transfusions are continued on a daily basis until one of the following stop criteria is met: (1) evidence of recovering bone marrow function as evidenced by a circulating PMN count of greater than  $500/\text{cm}^3$  and rising; (2) an afebrile condition after at least four PMN transfusions /24/; or (3) rapidly progressive disease without hope of recovery, or removal of patient permission.

#### Donor Evaluation

Because of the extensive manipulation of donors with either CFC or FL leukapheresis techniques, an extensive medical examination is performed to assure that they are in good health prior to donation. Donors must be over 18 years of age and under 65 and in good health as verified by a complete medical history and physical examination performed by one of the physicians on the Hematology-Oncology Service. The donor must have good superficial arm veins for ease



in starting the intravenous lines. In particular, there must be no history of anemia, easy bleeding from any cause, hypertension, or cardiovascular disease. Laboratory tests including complete blood count, platelet count, prothrombin time, partial thromboplastin time, SMA-12, and chest x-ray are done on each donor. If the donor is over 35 years of age, an electrocardiogram is also performed. All donors are required to have a type and cross match with the recipient for two reasons: (1) In both procedures, from 100 to 150 ml of red blood cells are inadvertently transfused with the granulocytes. ABO compatibility insures that major red blood cell transfusion reactions do not occur. (2) Morse et al /25/ showed that granulocytes harbor ABO antigens on their surface and that ABO incompatibility results in decreased granulocyte survival in animal recipients. Rh antigens are not present on granulocytes and Rh compatibility should be considered only if the recipient is a young Rh negative female in whom future pregnancies are anticipated.

Leukoagglutinin and lymphocytotoxicity compatibility has been looked at by a number of workers, and although Eyre et al /26/ demonstrated a slightly decreased one hour post-transfusion recovery, we have demonstrated that this does not adversely affect the clinical effectiveness of the PMNs transfused. HL-A matching is not routinely performed because of the expense involved and because several studies have resulted in no clinically significant benefit from transfusing HL-A matched granulocytes. /27/

The overall side effects of the leukapheresis on donors are extremely rare and when encountered are of a transient, benign nature. The overall donor reaction rate at LAMC from more than 600 donations was less than 6.1% and consisted mainly of transient chills, pruritus, and low grade fever (Table 3). These symptoms were easily controlled with antihistamines.

#### **Clinical Effectiveness of Granulocyte Transfusion**

Currently, only four major studies in the literature address themselves to the clinical effectiveness of granulocyte transfusion therapy. /28,29,30,31/ The first study in 1975 by Higby et al /28/ showed that in clinically septic, neutropenic patients, five of 19 control patients treated

with triple antibiotic therapy alone survived to day 20, whereas 15 of 17 patients receiving FL granulocytes and triple antibiotic therapy survived to day 20 (Table 5). Herzig et al /29/ reported on a prospectively randomized trial in 27 neutropenic patients with 30 episodes of gram negative septicemia, all culture proven. The control group was treated with appropriate antibiotic therapy only; the transfusion group was treated with the same antibiotic therapy and CFC or FL collected PMNs. Five of 14 patients in the control group survived and 12 of 16 in the transfused group survived. Analysis of the data revealed the most important factor to be the recovery of the bone marrow. Five of six patients in the control group where early marrow recovery (by day 10) was encountered survived, and 4 of 4 patients in the granulocyte transfusion group where the marrow recovered survived. Herzig et al /29/ concluded that granulocyte transfusion complement appropriate antibiotic therapy in culture-proven, septic, neutropenic patients.

TABLE 5  
CLINICAL EFFECTIVENESS OF GRANULOCYTE TRANSFUSIONS

Study	Overall survival		Survival (blood culture plus patients)		Survival (blood culture minus patients)	
	Control	PMN *	Control	PMN *	Control	PMN *
Higby et al	5/19	15/17	...	...	...	...
Herzig et al	5/14	12/16	5/14	12/16	...	...
Alavi et al	25/38	18/22	10/19	11/14	15/19	7/8
Vogler et al	2/13	10/17	2/13	10/17	...	...
Congdon et al	...	75/95	...	26/37	...	49/58

\* PMN = polymorphonucleated granulocyte

Alavi et al /30/ demonstrated similar survival: 55% of 19 patients treated with only antibiotic therapy survived to day 20, and 79% of patients treated with appropriate antibiotic therapy plus granulocyte transfusion therapy survived to day 20. Volger et al /31/ noted that 2 of 13 patients

treated with triple antibiotic therapy survived to day 20 when the criteria for neutropenia was 300 PMN/cm and 10 of 17 patients treated with antibiotics plus PMN transfusions survived to day 20. /31/

Survival data experienced at LAMC are similar to the experience in the above reported studies. Seventy-nine neutropenic patients were treated for 95 episodes of clinical sepsis with combination antibiotics and granulocyte transfusions. Survival to day 21 was noted in 75 of the 95 episodes overall and in 26 of 37 episodes where blood cultures were positive for pathogenic micro-organisms. Patient survival was associated with bone marrow recovery in 53 of 55 episodes and death occurred in 18 of 40 cases where the marrow did not recover. Survival was most closely associated with marrow recovery in the group of blood cultures positive for pseudomonas and fungus. Although the group with blood culture positive for other organisms had increased overall, survival marrow recovery did not correlate with survival (Table 6). Pretreatment of donors with corticosteroids resulted in increased granulocyte yields, similar recipient survival, and a trend toward fewer donor reactions when compared to a group of unstimulated donors.

TABLE 6  
RELATIONSHIP OF PATIENT SURVIVAL TO BONE MARROW RECOVERY

Patient subgroup	Episodes	Survived $\geq$ 20 days		Survived < 20 days	
		$\geq$ 500 Neutrophils	$\leq$ 500 Neutrophils	$\geq$ 500 Neutrophils	< 500 Neutrophils
Pseudomonas and/or fungus	14	7	0	0	7
Other positive blood cultures	23	9	9	1	4
Blood culture negative	58	37	13	1	7
<b>TOTAL</b>	<b>95</b>	<b>53</b>	<b>22</b>	<b>2</b>	<b>18</b>



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## HODGKIN'S DISEASE - CURRENT CONCEPTS

MAJ David R. Gandara, MC

Lymphoreticular tumors were first described in 1832 when Thomas Hodgkin reported seven patients with an affection of "the absorbent glands and spleen." He characterized these patients only by correlating clinical findings and gross anatomy because microscopic examination was virtually unknown.

In 1865, Wilks redefined this condition as a specific entity - Hodgkin's disease. Around 1900, Reed and Sternberg detailed the gross anatomic and microscopic features of Hodgkin's disease, and discovered the giant cells characteristic of the disease. Sternberg found tuberculosis in eight of 13 patients at autopsy and felt that Hodgkin's disease was an unusual form of this disorder. While Reed recognized this as coincidental, she also felt that Hodgkin's disease was of infectious origin.

Ninety-seven years after the original description by Hodgkin, the tissue sections on his seven patients were restudied. Only three of those patients had what we now accept as Hodgkin's disease. Two had other malignant lymphomas, one had tuberculosis, and one had syphilis. Considering the difficulties that often arise in differentiating this disease, Thomas Hodgkin did a remarkable job from only gross anatomic and clinical findings.

The etiology of Hodgkin's disease has always intrigued investigators. The role of heredity and environment remain unclear, although each certainly plays a part in susceptibility to the disease.

Age is an important factor. Some workers have felt that Hodgkin's disease is really a heterogeneous group of three subtypes based not as much on histology as on age. The first subtype is childhood Hodgkin's disease, the second is in the 20 to 30 year old group, and the third in old age. Childhood Hodgkin's disease occurs mainly in males - 91% according to a study by Strum and Rappaport. /1/

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They also reported a high incidence of nodular sclerosis (63%), although this has not been confirmed in other reports. The male predominance decreases between ages 10 to 20, suggesting possible hormonal influence.

The Hodgkin's disease of young adults has an equal sex distribution, but nodular sclerosis accounts for more than two-thirds of the female cases. It has been proposed that the Hodgkin's disease of young adults resembles a chronic granulomatous inflammation, while that of the older population acts more like a true malignancy. /2/

Familial Hodgkin's disease is rare, with less than one hundred reported families in the literature. There is a two to three-fold increase in risk with an affected family member. The possible role of the HL-A system has been investigated. There appears to be an increase, particularly in the W5 antigen in some studies. Of interest is the fact that this antigen has also been reported to occur with increased frequency in patients with infectious mononucleosis. /3/

It is known that in animal lymphoid neoplasms external factors can act as tumor-inducing agents. The geographic variation with Burkitt's lymphoma, highly associated with the Epstein-Barr (EB) virus, is a human example of this. The EB virus also plays a causative role in infectious mononucleosis. Infectious mononucleosis is an intense, self-limited lymphoproliferation. Histologically, it will occasionally contain bizarre binucleated cells resembling Reed-Sternberg cells. It has been speculated that infectious mononucleosis is the successful host response to a virus. If so, the different subtypes of Hodgkin's disease might represent varying degrees of the body's ability to fight off this viral agent. Case reports have described infectious mononucleosis preceding or merging into Hodgkin's disease. /4/ An increase in EB virus antibody has been reported in Hodgkin's disease itself. This increase is associated with symptoms of longer duration, more advanced disease, lymphocyte-depleted histology, and shorter survival. /5/

Thus, it has been suggested that Hodgkin's disease is an unsuccessful response to a virus of low virulence and

infectivity in a host with impaired immunity. Gross /6/ in 1966 suggested that there was an increase in the incidence of Hodgkin's disease in teenagers after removal of lymphoid tissue, e.g., tonsillectomy and appendectomy. Vianna /7/ felt the incidence increased two to three times following tonsillectomy. Other studies have not substantiated this finding. In 1971, he described an extended epidemic of Hodgkin's disease in a high school in Albany, New York, in which nine cases occurred among one family and close friends over a period of two decades. Further follow-up revealed that a total of 31 cases could be linked to this group.

Early workers found that a large number of patients with Hodgkin's disease had negative tuberculin skin tests, even in active tuberculosis. These findings led to a large body of information looking at the immune response in Hodgkin's disease.

Humoral immunity is intact in the untreated patient. Studies have shown slightly elevated IgG levels with a tendency for IgA and IgM to be low. Hypogammaglobinemia is rare.

In contrast, a defect in cell-mediated immunity is often found. Delayed homograft rejection occurs in two-thirds of patients. Kaplan /8/ reported that even stage I patients had decreased skin test positivity to dinitrochlorobenzene (DNCB). Therefore, the question arose as to whether the defect in cellular immunity occurs because of Hodgkin's disease, or whether it precedes the disease and may be causative. In a retrospective analysis of Kaplan's data, it was found that his patients were tested after or during radiation therapy. Studies by Brown et al /9/ in untreated patients showed no immunologic defect.

In 1972, Corder et al /10/ studied the transformation of lymphocytes with phytohemagglutinin (PHA) from patients with Hodgkin's disease. There was no difference between the earlier stages (I, II, and III), but patients with advanced disease (stage IV) had a much lower transformation. There was no correlation with the clinical course of the disease, and no differences were found among the various histologic subtypes. In another study by Young et al /11/, skin test anergy was seen only in patients with advanced disease, particularly in the presence of symptoms.



These and other studies have led to the conclusion that the defect in cellular immunity is a result of advanced Hodgkin's disease, rather than its cause. It is interesting, however, that autoimmune diseases have long been associated with the development of lymphoma. In particular, the associated diseases are rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's disease. Also of interest is the association of drugs, especially Dilantin®, with malignant lymphomas and pseudolymphomas. Dilantin® causes a megaloblastic anemia by a maturation arrest of proliferating cells in the bone marrow. It is not known what part this might play in a transition to lymphoma.

#### HISTOPATHOLOGY

Hodgkin's disease has been recognized as a distinctive process since the reports of Sternberg in 1898, and Reed in 1902. Although it requires the presence of Reed-Sternberg cells, their presence alone is not sufficient for a diagnosis. Cells resembling Reed-Sternberg cells have been described in a number of other conditions, from infectious mononucleosis to Burkitt's lymphoma, immunoblastic lymphadenopathy, pseudolymphoma from Dilantin®, and other non-Hodgkin's lymphomas. /12/ It is only when these characteristic multilobed giant cells are seen in the proper cellular and architectural setting that they become pathognomonic for Hodgkin's disease. This distinctive architectural setting includes a variable proportion of presumed reactive lymphocytes, plasma cells, eosinophils, neutrophils, histiocytes, and fibroblasts.

This variability into several rather distinct patterns led to the first attempt at a subclassification by Jackson in 1937 and Jackson and Parker in 1944. This classification had three subdivisions: paraganuloma, granuloma, and sarcoma. Paraganuloma had a predominance of lymphocytes and was associated with a good clinical course and long survival. Granuloma had islands of abnormal cells surrounded by bands of interconnecting collagenous tissue. The disease was usually mild and often localized to the mediastinum. A recognized subtype of granuloma had a higher proportion of malignant cells and a worse prognosis. Sarcoma had a

predominance of malignant elements with many Reed-Sternberg cells and a poor prognosis. With the use of this classification, only 10% of cases fell into either the favorable paraganuloma subtype, or sarcoma, the poorest prognostic category.

#### Lukes and Butler Subclassification

In 1966, the Lukes and Butler subclassification was published. It made use of two key observations. The first was the finding that survival paralleled the ratio of what morphologically appeared to be benign lymphocytes to the number of abnormal mononuclear cells and Reed-Sternberg cells. The second observation was that survival was improved in patients with biopsies showing sclerosis. This sclerosis was of a particular pattern which they termed nodular sclerosis. This subclassification had four distinctive types, each with its own clinical and histologic characteristics: (1) lymphocyte predominant; (2) nodular sclerosis; (3) mixed cellularity; and (4) lymphocyte depleted.

#### Lymphocyte Predominant

A biopsy of this subtype shows a homogeneous background of well-differentiated lymphocytes similar to lymphocytic lymphoma, except for the presence of occasional Reed-Sternberg cells. Eosinophiles and plasma cells are rare and significant fibrosis is absent.

#### Nodular Sclerosis

The nodular sclerosis category has two characteristics: (1) the presence of a variant of the Reed-Sternberg cell with cytoplasmic clear spaces, the so-called lacunar cell, and (2) that of broad bands of collagen surrounding cellular islands. Cases with minimal sclerosis, but with many lacunar Reed-Sternberg cells, have been described and are called the cellular or presclerotic phase of nodular sclerosis. In serial biopsies of the same patient, this cellular phase has been shown to subsequently develop extensive sclerosis. /13/

#### Mixed Cellularity

In the mixed cellularity subtype, Reed-Sternberg cells are usually more numerous than in the lymphocyte predominant and nodular sclerosis subtypes. There is a mixture of many reactive elements, usually eosinophiles and plasma cells, but with fewer reactive lymphocytes. Areas of fibrosis and necrosis may be seen.

#### Lymphocyte Depleted

The lymphocyte depleted subtype has even fewer lymphocytes. There are two forms. One is called the reticular form, which is hypercellular with a vast majority of elements being bizarre malignant cells. This is equivalent in the old terminology to Hodgkin's sarcoma. The second form is termed diffuse fibrosis in which the tissue is hypocellular with a diffuse network of fibrosis. Reed-Sternberg cells may be rare. Clinically, patients with these two forms may present differently. With the reticular form, patients may have bulky, rapidly progressive disease, and death may occur as a direct result of proliferation of the disease in vital organs. In contrast, diffuse fibrosis more often presents as a febrile, wasting illness, with little adenopathy, and with death from infection due to immunodeficiency. /14/

Progression from a less malignant to a more malignant histology has been well-documented. Serial biopsies of the same patient have shown lymphocyte predominant histology which progressed to mixed cellularity or the lymphocyte depleted form. Of the four subtypes, nodular sclerosis most often retains its distinct histology. This occurred in 91% of the cases as reported by Strum and Rappaport. /13/ In their study of 13 patients with the lymphocyte predominant type, four patients subsequently developed mixed cellularity, and three developed lymphocyte depleted histology. /13/ At presentation, from 10% to 20% of cases are unclassifiable.



## CLINICAL FEATURES

Almost 150 years have passed since Thomas Hodgkins wrote "On Some Morbid Appearance of the Absorbent Glands and Spleen." Since then; a great deal has been learned about the clinical features of Hodgkin's disease.

Superficial lymph nodes are involved in approximately 90% of cases. Cervical lymph nodes are found in 60% to 80%, axillary nodes in 10% to 20%, and inguinal nodes in 10% to 15%. In contrast to the adenopathy of chronic lymphocytic leukemia which is usually symmetric, in Hodgkin's disease it is often asymmetric.

Mediastinal Hodgkin's disease is found in 5% to 10% of all patients on presentation, but may eventually develop in over one-half of the patients. Most commonly, this form is seen in young women with the nodular sclerosing subtype. With mediastinal disease 70% will have positive right supraclavicular nodes, because of mediastinal lymphatic drainage. /15/ The main complications of mediastinal Hodgkin's disease are vascular compression such as the superior vena cava syndrome, and pulmonary parenchymal involvement.

Hodgkin's disease of the lung is found clinically in about 30% of patients. Unexplained shortness of breath or a nonproductive cough may be the only manifestations. The lungs can become involved either from contiguous spread of hilar involvement, or through hematogenous dissemination. This differentiation is of utmost importance because contiguous spread may be treated as local disease, while hematogenous spread is obviously stage IV disease and requires systemic therapy. The appearance of contiguous spread is usually that of hilar adenopathy with a fan-like pattern radiating out from the mediastinum. Hematogenous spread results in multiple intraparenchymal nodular infiltrates. These nodules may cavitate, especially with rapidly growing disease, and mimic infectious cavitory disease of the lung. /16/ After treatment, calcifications may also develop. Pleural effusion is found at autopsy in 60% of patients with intrathoracic Hodgkin's disease, although clinically the incidence is much less.

The heart and pericardium are involved less commonly in Hodgkin's disease than in non-Hodgkin's lymphomas. Involvement occurs in approximately 8% of patients and is usually attributable to contiguous spread from the mediastinum. /17/

The reported frequency of retroperitoneal disease varies tremendously depending on the extent of diagnostic evaluation, from 5% in clinical studies to 42% after staging a laparotomy. /15,18/

Many types of intraabdominal cancer spread from the lymphatics to the thoracic duct with involvement of the left supraclavicular nodes, the so-called Virchow's node. These nodes are frequently involved with abdominal Hodgkin's disease, and the presence of a positive left supraclavicular node should alert the clinician to the possibility of retroperitoneal disease. This dissemination of Hodgkin's disease was demonstrated by cytology performed after catheterization of the thoracic duct. /19/

The complications of retroperitoneal Hodgkin's disease are related to obstruction and infiltration. Obstruction of the ureters is not uncommon and is usually responsive to local irradiation. Intestinal obstruction is less common and occurs because of massive mesenteric and peritoneal spread. The first manifestation of gastrointestinal involvement may be a malabsorption syndrome. Clinically, the picture resembles sprue, but the villous atrophy may or may not be present on biopsy. Well-documented celiac disease has been reported to precede gastrointestinal Hodgkin's disease by periods of 20 to 30 years. The other major complication from retroperitoneal Hodgkin's disease is compression of the spinal cord. This complication occurs from spread by perineural lymphatics into the epidural space. The earliest symptom is usually back pain which is often radicular. Gradual motor dysfunction and sensory loss may follow. Sphincter control is the last function lost and usually indicates advanced cord damage. Spinal cord compression occurs in up to 5% of patients with Hodgkin's disease. /20/ The thoracic spine is the most common site, probably related to mediastinal spread of Hodgkin's disease. Decompressive laminectomy followed by radiation therapy is effective in about 50% of

cases. Radiation without previous laminectomy carries some risk because of acute edema of epidural tissue.

Although liver involvement is not common in Hodgkin's disease at the time of presentation, it increases with duration and progression of disease to 60% in autopsy studies. /21/ A positive diagnosis of hepatic Hodgkin's disease may be difficult to make and the correlation with clinical suspicion is not good. Staging laparotomies has greatly increased the ability to diagnose hepatic involvement of Hodgkin's disease.

Bone marrow involvement occurs in 5% of cases. Hodgkin's disease infiltrates the bone marrow focally, and can be extremely difficult to demonstrate. Bone marrow aspirates have a poor yield and bilateral posterior iliac crest biopsies should be done.

Involvement of the central nervous system with Hodgkin's disease is relatively rare, occurring in less than 2% of patients. There is a predilection for the basilar area, resulting in a high percentage of patients with cranial nerve involvement. The third, sixth, and seventh cranial nerves are most frequently involved. Optic nerve atrophy has also been reported from local infiltration of the nerve sheath. /19/

Constitutional symptoms such as weakness, fatigue, anorexia, and pruritus are particularly common in Hodgkin's disease. Night sweats, fever, and weight loss are also common and hold a particular significance. Within certain limitations, they comprise the "B" designation for systemic symptoms in Hodgkin's disease. This "B" symptomatology correlates with extent of disease, response rate, and duration of response. The "B" symptoms are:

- Unexplained weight loss (greater than 10% in six months)
- Unexplained fever (greater than 38 degrees centigrade)
- Night sweats

Pruritus was removed as a qualifying symptom although in certain patients it does appear related to disease activity. Pruritus occurs in up to 25% of patients, and is more common with bulky mediastinal or abdominal disease. Fever occurs as an unexplained phenomenon in 30% of patients. It may be cyclic



with a few days of fever alternating with an afebrile interval (the so-called Pel-Epstein fever). Its exact cause is unknown, but pyrogenic material has been found in urine concentrates of patients with Hodgkin's disease. In some patients, this pyrogen has disappeared in remission and reappeared during relapse. Another explanation for fever is related to circulating tumor cells. In one study, fever was present in 90% of patients with circulating tumor cells and in only 27% of those with negative cytology. /19/

Alcohol-induced pain in Hodgkin's disease was first described in 1950, and is reported to occur in almost 30% of patients. Characteristically, the pain follows ingestion of even a small amount of any alcoholic beverage, occurs within a few minutes of ingestion, and may last for several hours. Usually the pain is localized to an area of involvement. It has been reported to disappear after therapy and to reappear with recurrence of disease. /17/

#### STAGING

With improvement in radiation therapy and the advent of successful combination chemotherapy, accurate staging has become even more important in Hodgkin's disease. Stage of disease is the most important determinant of prognosis in an individual patient and is crucial in guiding therapeutic decisions. Accurate staging is also essential for meaningful comparisons between series of patients reported in the literature. The Ann Arbor staging classification of 1971 (Table 1) makes a clear distinction between clinical and

TABLE 1  
LYMPHOMA STAGING CLASSIFICATION

Rye	Ann Arbor	Involvement
I	I	Single lymph node region
II	II	Two or more regions, one side of diaphragm
III	III	Lymph nodes on both sides of diaphragm
IV	IV	Diffuse extralymphatic involvement
IV	I <sub>E</sub> *	Single extralymphatic site
IV	II <sub>E</sub> *	Extralymphatic site and nodal involvement, one side of diaphragm
IV	III <sub>E</sub> *	Extralymphatic site and nodal involvement, both sides of diaphragm

\*I<sub>E</sub> = Extension to a single extralymphatic site

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pathologic staging and is more accurate in describing extent of extranodal disease. This classification makes extensive use of a letter system to designate sites of extranodal spread: H = Liver; M = Bone marrow; D = Skin; S = Spleen; P = Pleura; O = Osseous; L = Lung; N = Lymph node. As can be seen in this comparison, extension to a single extralymphatic site is designated as "I<sub>E</sub>" by the Ann Arbor classification, while the same patient would be described as having stage IV disease under the old Rye classification.

The diagnostic evaluation begins with a careful history, with special emphasis on unexplained fever, night sweats, or weight loss. Physical examination should stress evaluation of peripheral lymph nodes and assessment of liver and spleen size. Routine chest x-ray should be followed by whole lung tomography if mediastinal or hilar adenopathy is suspected. Laboratory tests of special importance include: complete blood and platelet count, serum alkaline phosphatase, erythrocyte sedimentation rate, and serum copper. Radioisotopic studies such as liver-spleen scan and gallium scan have been disappointing in the staging evaluation of Hodgkin's disease. Laparotomy series have shown a poor correlation between liver-spleen scan and histology from liver biopsy and splenectomy. /22/ When gallium 67 citrate scanning was developed, there was great hope that it would be an accurate, noninvasive method of staging patients with lymphoma. Despite several initial favorable reports, it now appears gallium scanning has neither the sensitivity nor the specificity necessary for a reliable staging procedure. Bone marrow evaluations should be done early in the staging, despite the fact that the yield is low. If positive, establishing the presence of stage IV disease, invasive procedures such as staging laparotomy may be unnecessary.

The lymphangiogram is an essential part of staging even when a laparotomy is planned. Adequacy of surgical sampling can be determined at the time of laparotomy by a repeat film showing removal of suspected nodes. After staging is complete, the lymphangiogram is of value to the radiation therapist in determining treatment ports. An additional asset is the ability to follow the previously opacified lymph nodes with serial films after therapy. Unsuspected relapse may be demonstrated by a change in

nodal status. Lymphangiography, however, is not a definitive procedure in the assessment of abdominal disease. Certain areas such as mesenteric nodes, the splenic hilar nodes, the celiac axis, and the paraaortic nodes above the L-2 level are not visualized by the lymphangiogram. Lymphangiography has an 85% to 90% correlation with staging laparotomy when the study is nonequivocal. However, up to 20% of studies will fall into this category, even in the best of medical centers.

Laparotomy remains the most accurate method of delineating the extent of intraabdominal Hodgkin's disease. The routine use of laparotomy has allowed several clinical correlates to be established.

As expected, almost all patients with a positive lymphangiogram have a positive staging laparotomy. However, of patients with "B" symptomatology and clinical disease apparent only above the diaphragm (1B and 2B), 40% with a negative lymphangiogram will have positive abdominal findings. /23/ This finding establishes "B" symptoms as an important predictor of disseminated disease. Laparotomy series have demonstrated that splenic enlargement on examination or scan is not necessarily an indication of involvement with Hodgkin's disease. Fifty percent of enlarged spleens will be negative at laparotomy, while 25% of clinically negative spleens will be involved with Hodgkin's disease.

An important clinical observation from laparotomy series is the correlation between splenomegaly and hepatic involvement. Of the 50% to 75% of palpable spleens that are positive at laparotomy, one half will have associated disease in the liver. If the spleen is not palpable, only 5% will have hepatic involvement at laparotomy. /24/ If the spleen is negative histologically, there is virtually no chance of hepatic Hodgkin's disease.

The importance of splenectomy at the time of staging laparotomy remains controversial. Splenectomy allows modification of radiation therapy ports, minimizing radiation damage to the left kidney and left lung. In addition, there is evidence that splenectomized patients have improved hematologic tolerance to subsequent chemotherapy. /25/ Despite these benefits, recent reports of



fulminant septicemia in children previously splenectomized for Hodgkin's disease have tempered the enthusiasm for this procedure. /26/

#### RADIATION THERAPY

Irradiation has been used in the treatment of Hodgkin's disease for more than 50 years. Considerable progress has been made in radiation therapy since that time, following acceptance of several technical principles. /27/ First, it has been established that each lymph node region must be treated in its totality. Partial irradiation of an involved lymph node chain results in a higher incidence of recurrence. Furthermore, these recurrences may be extremely difficult to treat because of the risk of overlapping previously treated fields. Megavoltage irradiation should be used to reduce scatter and to avoid severe skin reaction. With megavoltage radiation, the minimal dose which must be delivered to an involved area is approximately 4,000 R in four weeks. At this dose, the local recurrence rate is 4%. Below this level, the incidence of local recurrence rises progressively. /28/ Lastly, prophylactic or extended field irradiation is beneficial with certain cell types and presentations of Hodgkin's disease. This is true because even the most sophisticated staging evaluation remains a gross estimate of extent of disease.

Radiotherapy fields have been standardized for local field, extended field, and total nodal irradiation. The standard single field for the supradiaphragmatic region is called the mantle field. This includes the bilateral neck and axillary regions and the hilar mediastinal nodes to the level of the diaphragm. For the subdiaphragmatic region, a field in the form of the inverted Y covers the paraaortic, iliac, and inguinal areas. If indicated, the inverted Y can be joined to a field covering the spleen and splenic hilum. These wide field irradiations are generally well tolerated if the patient has a rest period of four weeks between the mantle and inverted Y. However, total nodal irradiation covers 60% of the bone marrow in the target volume, and if thrombocytopenia or leukopenia occur, the

rest period may have to be extended. Prominent nausea, vomiting, diarrhea, and weight loss during treatment may also cause delays to the inverted Y portal. Complications also arise because of radiation damage of structures underlying the treatment ports. Possible complications include radiation pericarditis, myocarditis, and pneumonitis. Use of current treatment techniques reduces the incidence of these complications below 5%. Radiation-induced hypothyroidism occurs somewhat less frequently. Lhermitte's syndrome is a shooting pain similar to electric shock with flexion of the neck. It occurs when doses over 3,000 to 3,500 R are delivered to the cervical cord.

Radiotherapy is the treatment of choice for early Hodgkin's disease. In the asymptomatic patient with local disease and a favorable histology (lymphocyte predominant or nodular sclerosis subtypes), local or extended field radiotherapy offers a five year disease-free survival rate of 85% to 90%. With "B" symptomatology (1B or 2B) and unfavorable histology (mixed cellularity or lymphocyte depleted subtypes), many centers recommend total nodal irradiation plus six cycles of combination chemotherapy, even with apparent localized disease. /29/

The role of radiation therapy in the management of stage III Hodgkin's disease is controversial. /23/ Certain subsets of patients with stage III disease, those with "B" symptoms or unfavorable histology do poorly with radiation therapy alone. As a result, total nodal irradiation is recommended only for stage III-A patients with favorable histology. For stage III-B or with unfavorable histology (mixed cellularity and lymphocyte depleted subtypes), total nodal irradiation followed by combination chemotherapy is the recommended treatment. Combination chemotherapy is the treatment of choice for stage IV Hodgkin's disease.

#### CHEMOTHERAPY

Tremendous advances have been made in the chemotherapeutic approach to advanced Hodgkin's disease since the introduction of nitrogen mustard for clinical use in 1946. Initially, single agent chemotherapy was utilized for patients with advanced disease. A wide variety of agents

was shown to have activity in Hodgkin's disease. As single agents, however, complete responses were few and duration of response was short. There were few long-term survivors. During the 1960s, the concept of combination chemotherapy was developed. This utilizes multiple agents in an attempt to gain an additive effect without overlapping toxicity. The MOPP regimen (Table 2) reported in 1970 remains the standard for the treatment of disseminated Hodgkin's disease. /30/

TABLE 2  
MOPP CHEMOTHERAPEUTIC REGIMEN

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M = Nitrogen mustard – 6 mg/M <sup>2</sup> , intravenously, on day 1 and 8
O = Vincristine – 1.4 mg/M <sup>2</sup> , intravenously, on day 1 and 8 (maximum single dose = 2 mg)
P = Prednisone – 40 mg/M <sup>2</sup> , orally, on days 1 through 14
P = Procarbazine – 100 mg/M <sup>2</sup> , orally, on days 1 through 14

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Of the original 43 patients who received MOPP for six months, 35 (81%) achieved a complete remission. Six additional patients had partial responses for a total response rate of 95%. The median duration of remissions was 36 months. The greatest impact of MOPP therapy, the potential for long-term, disease-free survival, is demonstrated in a recent ten-year progress report. In a series of 200 patients with advanced Hodgkin's disease treated with MOPP, over 50% remain in complete remission at five and 10 years. /31/ A number of clinical studies have investigated variations of the MOPP regimen by substitution or deletion of the various agents. Several regimens, particularly COPP (C = cyclophosphamide, O = vincristine, P = prednisone, P = procarbazine) and MVPP (M = nitrogen mustard, V = vinblastine, P = prednisone, P = procarbazine) appear to be equal to MOPP therapy. To date, no chemotherapeutic regimen has been shown to be superior. /32/ One interesting development has been the utilization of low dose radiotherapy to bulky areas of disease as an adjunct to combination chemotherapy. With the use of combination chemotherapy alone, patients have a tendency to relapse in areas of former bulky disease. The addition of low dose radiotherapy to these areas has improved disease-free survival in some studies. /33/



The use of maintenance therapy remains controversial in Hodgkin's disease. The most important factor appears to be careful restaging to assure that a complete remission has been obtained. When this has been done, no maintenance regimen has been shown to be consistently superior to MOPP chemotherapy alone. /32/

Despite these advances, almost one half the patients with advanced Hodgkin's disease treated with MOPP chemotherapy will eventually relapse. Recently, tremendous interest has been generated by a new combination regimen for MOPP failures. This regimen, ABVD (Table 3), utilizes four chemotherapeutic agents not included in the MOPP regimen.

TABLE 3  
ABVD CHEMOTHERAPEUTIC REGIMEN

---

A = Adriamycin - 25 mg/M <sup>2</sup> , intravenously, on day 1 and 14
B = Bleomycin - 10 mg/M <sup>2</sup> , intravenously, on day 1 and 14
V = Vinblastine - 6 mg/M <sup>2</sup> , intravenously, on day 1 and 14
D = Dacarbazine - 150 mg/M <sup>2</sup> , intravenously, on days 1 through 5

---

The ABVD regimen appears to be equal to MOPP both in complete remission rate and duration of response. In addition, cross resistance between the two regimens appears to be slight. /34/ Thus, the ABVD program is an effective regimen for patients who have failed on MOPP therapy.

It now appears clear that intensive treatment with radiation and chemotherapy can offer the possibility of cure for even disseminated forms of Hodgkin's disease. However, this aggressive therapy is not without potential risk. Recent studies have demonstrated a greatly increased incidence of second malignancy in patients receiving combined radiation and chemotherapy. /35/ The cause of the second malignancy is unclear, but the greatest risk appears to be limited to those patients receiving both forms of therapy. /36/ This risk emphasizes the need for accurate staging and careful selection of therapy to avoid over-treatment of this potentially curable disease.

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## THE NON-HODGKIN'S LYMPHOMAS: A SUMMARY

MAJ Hyatt P. DeGreen, MC

The non-Hodgkin's lymphomas (NHL) originally were divided into two basic groups: lymphosarcoma (LSA) and reticulum cell sarcoma (RCSA). It later became obvious that each group contained several subgroups with differing prognoses. Thus, in 1966 the Rappaport classification of the non-Hodgkin's lymphomas was introduced (Fig 1). Other classifications have since been proposed, but none has proven to be of greater clinical relevance.

In 1972, Jones et al studied the clinicopathologic correlation of 405 cases of NHL. Nodular lymphomas constituted 44% of the group and tended to cluster around a narrower age range than did the diffuse lymphomas; patients under 35 years of age and over 60 years of age were the most highly susceptible to a diffuse NHL. Localized extralymphatic involvement occurred more frequently in the diffuse than in the nodular lymphomas. Although the gastrointestinal tract was the most common site of involvement, bone, skin, pleura, thyroid, and cervix were also affected.

In Hodgkin's disease, nodular sclerosis directly affects the mediastinum in 50% to 75% of all cases; in non-Hodgkin's disease, there is no one type for which this is true. The incidence of mediastinal involvement for both diffuse and nodular NHL is reported as 15% to 20%.

Upper abdominal lymphadenopathy with or without mediastinal involvement and left lower neck lymphadenopathy is known to occur in Hodgkin's disease and was reported by Jones et al in 1972 to also occur in NHL. Left lower cervical or supraclavicular lymphadenopathy in association with periaortic involvement in the absence of mediastinal involvement (mediastinal skip) was observed in 40% of the nodular and 20% of the diffuse lymphomas. The increased tendency in nodular lymphomas was significant. In patients with NML and PDLL-N, mediastinal skipping occurred three times more frequently than did mediastinal involvement, and it



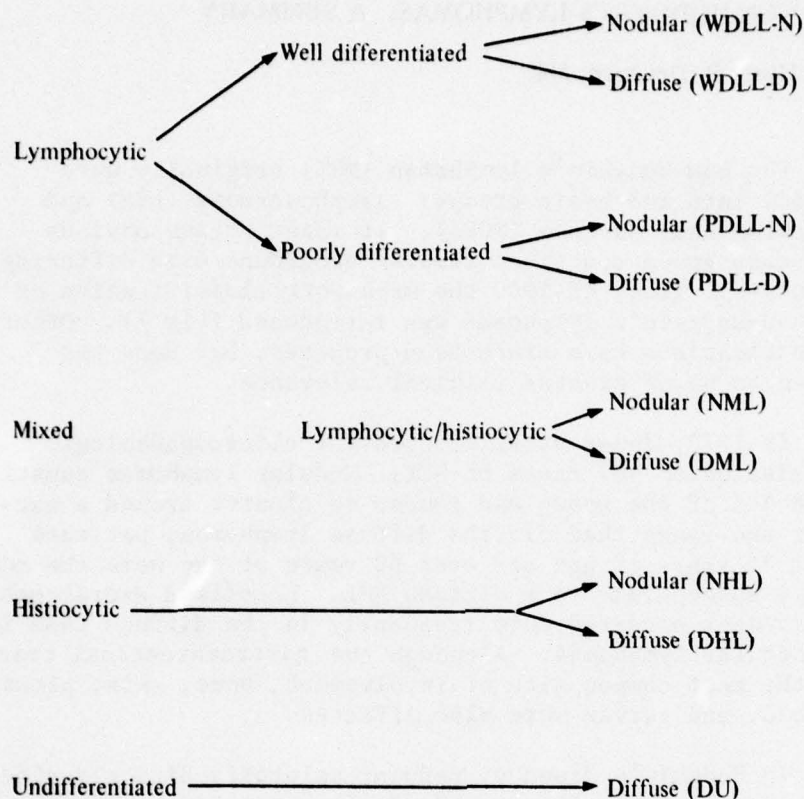


Figure 1. Rappaport classification of the non-Hodgkin's lymphomas.

correlated favorably with survival. Mediastinal skipping occurred least often in patients with DHL. Likewise, contiguous patterns of spread occurred with almost the same frequency as in Hodgkin's disease.

Results of the nonsurgical and surgical staging of NHL were reported by the National Cancer Institute; Chabner et al found no significant differences in the relative frequency of spread in bone marrow, liver, or by lymphangiography when they compared primary nodal sites in 135 patients to primary

extranodal sites in 35 patients. Table 1 shows that lymphangiography was positive in 90% of nodular and 66% of diffuse lymphomas. Positive lymphangiography correlated strongly with positive findings recorded at laparotomy or in liver biopsies done preoperatively.

TABLE 1  
YIELD OF NON-SURGICAL PROCEDURES  
IN STAGING NON-HODGKIN'S LYMPHOMA\*

	Lymphangiogram		Bone Marrow Biopsy		Percutaneous Liver Biopsy		Peritoneoscopy Liver Biopsy	
	no. +/no. tested	%	n. +/no. tested	%	no. +/no. tested	%	no. +/no. tested	%
Nodular								
PDL	38/42	90	19/48	40	14/45	31	6/28	21
Mixed	18/20	90	11/24	46	4/21	21	7/17	41
HIST	6/7	86	1/7	14	0/6	0	3/6	50
Total	62/69	90	31/79	39	18/72	25	16/51	32
Diffuse								
WDL	5/5	100	6/6	100	2/4	50	0/1	0
PDL	10/16	63	15/28	54	5/15	33	5/7	71
Mixed	6/7	86	2/6	33	1/4	25	2/5	40
HIST	21/37	57	6/39	15	2/33	5	3/26	12
Stem	3/3	100	4/7	57	0/3	0	0/1	0
Total	45/68	66	33/86	38	10/59	17	10/40	25

Abbreviations: WDL = well differentiated lymphocytic; PDL = poorly differentiated lymphocytic; Mixed = mixed lymphocytic-histiocytic; HIST = histiocytic; Stem = pleomorphic or stem cell lymphoma.

\* From Chabner BA, Johnson RE, Young RC, et al: Sequential non-surgical and surgical staging of non-Hodgkin's lymphoma. *Ann Intern Med* 85:149-154, 1976. Reprinted with permission of the authors and the publisher, Annals of Internal Medicine.

In general, a higher percentage of nodular lymphomas present initially with disseminated disease. The extent of the disease, however, appears to be independent of actuarial survival which is uniformly higher for nodular than for diffuse lymphomas (Fig 2). The one exception to this is the WDLL-D, which is considered to be synonymous with chronic lymphocytic leukemia. In contrast to Hodgkin's disease, "B" symptoms do not correlate with survival.

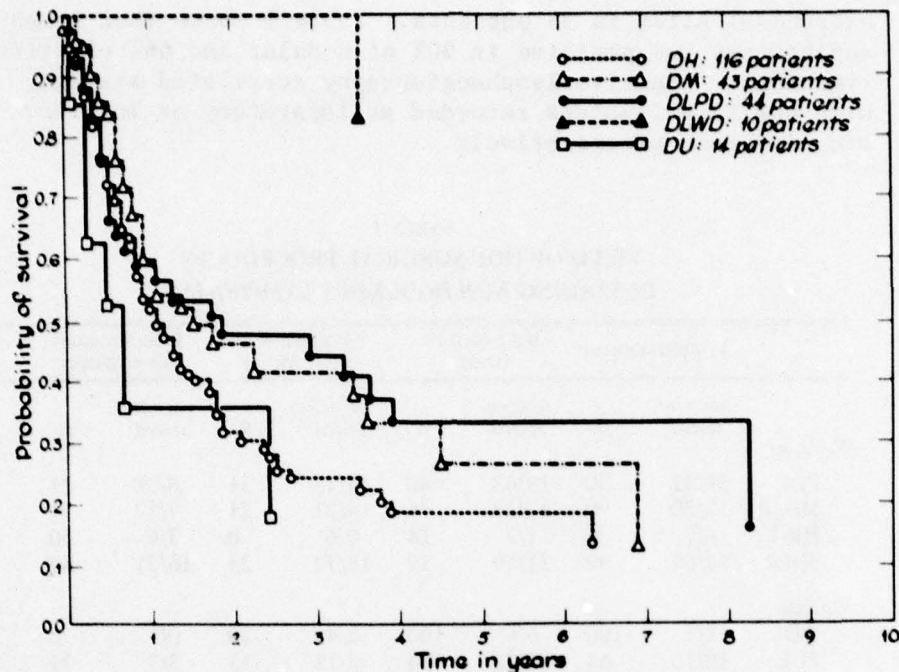


Figure 2. Actuarial survival for all patients in each histologic category of diffuse lymphoma. From Jones SE, Fuks Z, Bull M, et al: Non-Hodgkin's lymphomas - IV. Clinicopathologic correlation in 405 cases. *Cancer* 31:806-823, 1973. Reprinted with permission of the authors and the publisher, J.B. Lippincott.

The response of NHL to single agent chemotherapy is shown in Table 2. Fig 3 shows the actuarial survival for all patients in each histologic category of nodular lymphomas. Therapy for this group of patients was not standardized. It consisted of radiation therapy, sequential use of active single chemotherapeutic agents, or radiation therapy followed by sequential chemotherapy at relapse. Although complete responders to chemotherapy had longer survivals than did the partial responders with the same histology, a plateau of disease-free survival was never achieved.

As an extension of this experience, Portlock et al reported on the treatment of NHL with favorable histology. Sixty-three patients with stage IV WDLL-D, WDLL-N, NML, and PDLL-N were randomized to receive either CVP, CVP and total



lymphoid irradiation, or single alkylating agent with chlorambucil (SA). The actuarial probability of a complete remission was greater than 80% for all groups. The time required to achieve a complete remission was longer for SA patients (up to 40 months) than for other groups (up to 16 months). The authors were not able to assess the durability of the complete remission because the follow-up period for all patients was less than 48 months.

TABLE 2  
NON-HODGKIN'S LYMPHOMA-RESPONSE  
BY HISTOLOGIC CATEGORY TO SINGLE AGENT CHEMOTHERAPY\*

	Cytosan or Chlorambucil	Vincristine	Prednisone
<i>Nodular (all)</i>		9 (64% PR)	0 (57% PR)
NHL	28		
NML	31		
PDLL-D	48		
<i>Diffuse (all)</i>		0 (40% PR)	0 (22% PR)
DHL	5		
DML	13		
PDLL-D	22		

Abbreviations: NHL = Nodular histiocytic lymphoma; MNL = nodular mixed lymphoma; PDLL-N = poorly differentiated lymphocytic lymphoma - nodular; DHL = diffuse histiocytic lymphoma; DML = diffuse mixed lymphoma; PDLL-D = poorly differentiated lymphocytic lymphoma - diffuse.

\* CR expressed in %.

An important subgroup of patients considered to have a favorable histology are those with NML. Jones et al found that although projected survival is long, the disease-free intervals are short and require continued therapy with single agent chemotherapy. In 1977, Young et al of the National Cancer Institute reported that 77% of patients who underwent combination chemotherapy (six monthly courses of C-MOPP)

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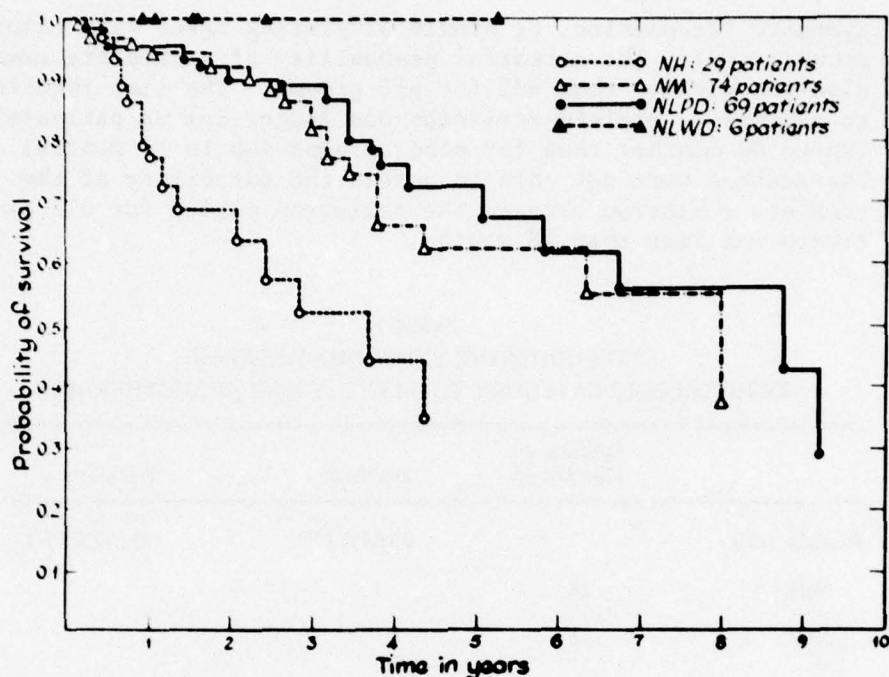


Figure 3. Actuarial survival for all patients on each histologic category of nodular lymphoma. From Jones SE, Fuks Z, Bull M, et al: Non-Hodgkin's lymphomas - IV. Clinicopathologic correlation in 405 cases. *Cancer* 31:806-823, 1973. Reprinted with permission of the authors and the publisher, J.B. Lippincott.

for advanced disease in NML achieved a complete remission. Of these patients, 78% have remained free of disease with no additional chemotherapy for periods up to eight years. The striking difference between NML and other favorable histologies is its long-term, disease-free survival. Predictable relapse appears to continue in the other groups despite early combination chemotherapy. A study made by Levitt et al and reanalyzed by Berd et al showed that of 15 patients with RCS, eight were reclassified as DHL under the Rappaport system. Six of these eight patients obtained complete remissions, with five of the six sustaining unmaintained remissions for more than five years. Additional experience with the poor prognostic group of DHL has shown significant prolongation of survival and suspected "cure" with combination chemotherapy (C-MOPP, BACOP, CHOP-BLEO - see Appendix).

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Schein et al in 1975 reported that a partial remission did not improve the overall survival of a poor prognostic group of patients; a complete remission was induced in only two of nine patients (22%) with PDLL-D treated with CVP combination therapy. Of the two patients in complete remission, unmaintained remissions were for nine and 31 months, respectively. The suggestion is that a complete remission in PDLL-D imparts the same significantly prolonged survival and possible cure as is possible with DHL. Prospective studies are currently in progress, using combination therapy similar to that used in DHL.

Interest in total body irradiation as treatment of advanced (stage III and IV) lymphocytic lymphomas was renewed at the National Cancer Institute in 1964. Early results were encouraging and a prospective trial was begun in 1966 by Canellos et al. In this trial, combination chemotherapy was compared to total body irradiation in the treatment of advanced lymphocytic lymphomas. No significant difference in the nodular lymphomas was found in the two treatment groups. Patients with PDLL-D treated with total body irradiation had a greater survival (up to 18 months of follow-up); however, the curves began to converge at 24 months and then lost their significance. The possible role of total body irradiation in the treatment of NHL is yet to be defined; its advantages over chemotherapy are its ease of administration and its low morbidity.

It has taken a decade for Rappaport's classification of the NHL to be generally accepted; it will likely take as long or longer for the clinical usefulness of later classifications to become apparent.

In 1971, Lukes and Collins introduced a classification of the NHL reutilizing the follicular center concept, based strictly on their morphological observations. The follicular (germinal) center origin of NHL has been substantiated at least in part with T and B cell markers. Fig 4 shows a comparison of the Rappaport with the Lukes and Collins classifications. Although the clinical usefulness of the Lukes and Collins classification remains to be defined, the morphologic conceptualization of the NHL deserves further study. Clearly, the convoluted cell type of PDLL-D, as it correlates with the T cell variety of childhood acute lymphocytic leukemia,



is now recognized, as is the distinct morphologic entity of immunoblastic lymphadenopathy.

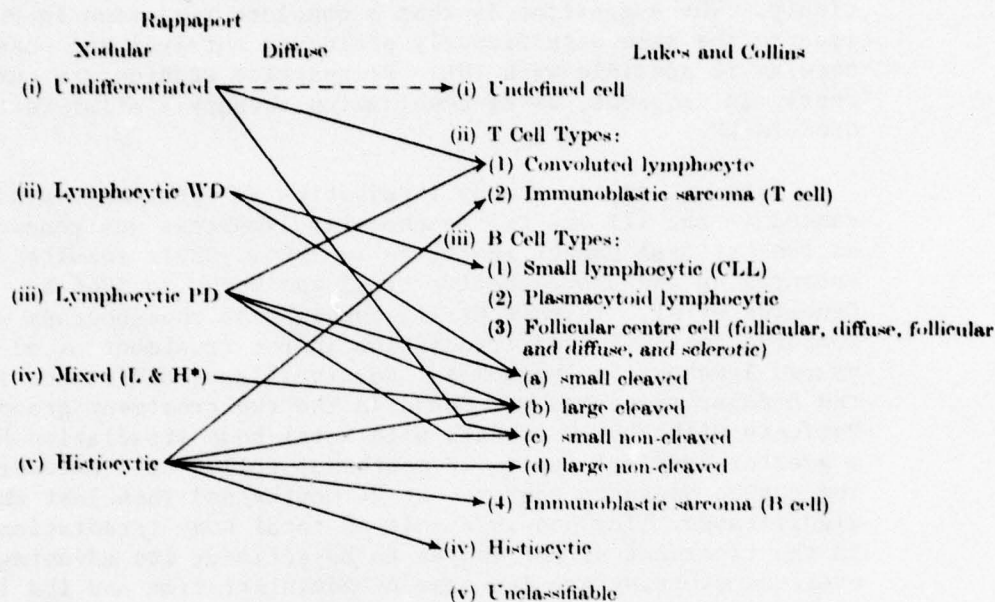


Figure 4. Comparisons of classifications. Asterisk (\*) indicates lymphocytic and histiocytic. From Lukes RJ, Collins RD: New approaches to the classification of the lymphomata. *Br J Cancer* 31 (Suppl 2): 1-28, 1975. Reprinted with permission from the authors and the publisher, H.K. Lewis & Co., Ltd.

Current research in cell surface markers may have prognostic significance in high risk patients with NHL. Bloomfield et al recently reported 75 cases of NHL in which clinical staging and treatment were standardized for all patients. All nodular lymphomas were B cells. And, in her series of PDLL-D, Dr. Bloomfield's B cell variety had a better prognosis (Table 3).

TABLE 3  
SEVENTY-FIVE CASES IN WHICH CLINICAL STAGING  
AND TREATMENT WERE STANDARDIZED FOR ALL PATIENTS

PDLL-D*	Number of patients	Percentage	Median survival
B cell	16	53	26 months
Null cell	9	30	5 months
T cell	5	17	Not analyzed

\*PDLL-D = Poorly differentiated lymphocytic lymphoma - diffuse.

#### Conclusions

The non-Hodgkin's lymphomas are a complexity of diseases. Although the natural history of the poor risk groups has been favorably altered, a large percentage of patients still succumb early to this disease.

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## APPENDIX

### DEFINITIONS

#### Chemotherapy

BACOP.....bleomycin, adriamycin, Cytosan®, Oncovin®,  
prednisone  
CHOP-BLEO.....Cytosan®, adriamycin (Hydroxyldaunomycin),  
Oncovin®, prednisone, bleomycin  
C-MOPP.....Cytosan®, vincristine (Oncovin®), prednisone,  
procarbazine hydrochloride  
CVP.....Cytosan®, vincristine, prednisone

#### Non-Hodgkin's Lymphomas

DHL.....diffuse histiocytic lymphoma  
DML.....diffuse mixed lymphoma  
DU.....diffuse undifferentiated  
NHL.....nodular histiocytic lymphoma  
NML.....nodular mixed lymphoma  
PDLL-D.....poorly differentiated lymphocytic lymphoma -  
diffuse  
PDLL-N.....poorly differentiated lymphocytic lymphoma -  
nodular  
WDLL-D.....well differentiated lymphocytic lymphoma -  
diffuse  
WDLL-N.....well differentiated lymphocytic lymphoma -  
nodular

## QUANTITATIVE PLATELET DISORDERS

MAJ Irwin B. Dabe, MC

Thrombocytopenia may be caused by a number of disorders that can be generally divided into two pathophysiologic etiologies: increased platelet destruction and decreased platelet production. In some clinical situations, both mechanisms operate simultaneously. The terms "idiopathic thrombocytopenia" (ITP) and "autoimmune thrombocytopenic purpura" (ATP) may be used interchangeably.

### INCREASED PLATELET DESTRUCTION

#### Immune Thrombocytopenias

*Platelet autoantibodies in ITP.* Idiopathic thrombocytopenic purpura is the most common cause of thrombocytopenia; patients with ITP comprise about 0.2% of all hospital admissions. /1/ Sixty to seventy percent of patients with ITP are less than 21 years and 45% are less than 15 years of age. In 1951, Harrington et al /2/ first reported the existence of a serum factor that was believed to be of etiologic importance in the disorder. Harrington injected himself with 250 ml of plasma from a patient with ITP. This resulted in a prompt drop in platelet count that reached a nadir in one to three hours and returned to normal in four to six days.

Fig 1 shows the effects of the transfusion of 50 ml of citrated blood or its plasma equivalent from 17 patients with ITP into healthy laboratory workers or patients with inoperable cancer. Harrington et al /2/ showed this thrombocytopenic factor to be a gamma globulin. In 1965, Shulman /3/ found the factor to be a species specific 7S gamma globulin that caused damage to autologous and homologous platelets. In 1969, Karparkin and Suskind /4/ demonstrated that the factor was an IgG immunoglobulin.

Subsequent work by Karparkin et al /5/ disclosed that:  
(1) Complement is not involved in the process. (2) The

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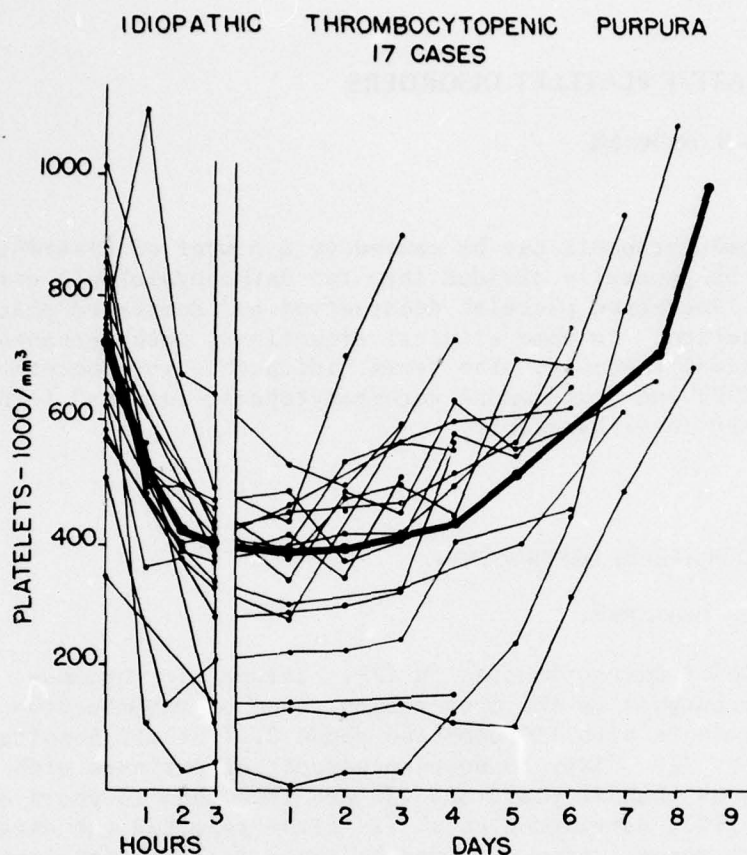


Figure 1. Thrombocytopenic effect produced by transfusing 500 cc of citrated blood or its plasma equivalent from 17 patients with thrombocytopenic purpura. Transfusions were given at "0" time. Recipients were healthy laboratory workers or patients with inoperable carcinoma. The mean effect is represented by the heavy line. From Harrington WJ, Minnich V, Arimura G: The autoimmune thrombocytopenias, in Tocantins LM (ed): *Progress in Hematology*, New York: Grune & Stratton, Inc., 1956, vol. 1, p. 174. Reprinted with permission from the authors and the publisher.

antibody is produced by spleen cells *in vitro*. Donnell et al /6/ found that the antibody produced by these spleen cells in *in vitro* cell culture binds to normal platelets, and that the antibody produced by the spleens of two patients with ITP saturated different sites on normal platelets, implying different antigen specificity for the antibodies produced by these patients. (3) The antibody causes lymphocyte transformation *in vitro* when the autologous platelets are present. /7/ (4) The antiplatelet antibody is not detectable in all cases of ITP. Many studies have shown that it is present

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in the serum only 60% to 70% of the time, although in a study by Prankherd /8/ in which a dextran agglutination method for measuring antiplatelet antibody was used, it was detected in about 85% of patients.

In 1975, Dixon et al /9/ developed a complement lysis inhibition assay for the quantitative measurement of IgG antibody on the surface of the platelets. They used an indirect method in which a known amount of rabbit antihuman IgG antibody is incubated with the platelets. The platelets with the attached antibody are removed and the amount of antibody left behind in solution is measured by incubating the solution with sheep red blood cells coated with IgG. Guinea pig serum is added as a complement source to measure the amount of lysis of sheep red blood cells (SRBC) produced.

Fig 2 shows that surface-bound IgG was easily detectable on platelets from normal patients as well as on platelets from patients with ITP but that the 16 normal patients tested had less than  $3 \times 10^{-13}$  grams of IgG/platelet whereas the amount of IgG on the surface of the platelets from 17 patients with ITP ranged from  $5 \times 10^{-13}$  grams/platelets to  $34 \times 10^{-13}$  grams/platelet with no overlap between groups.

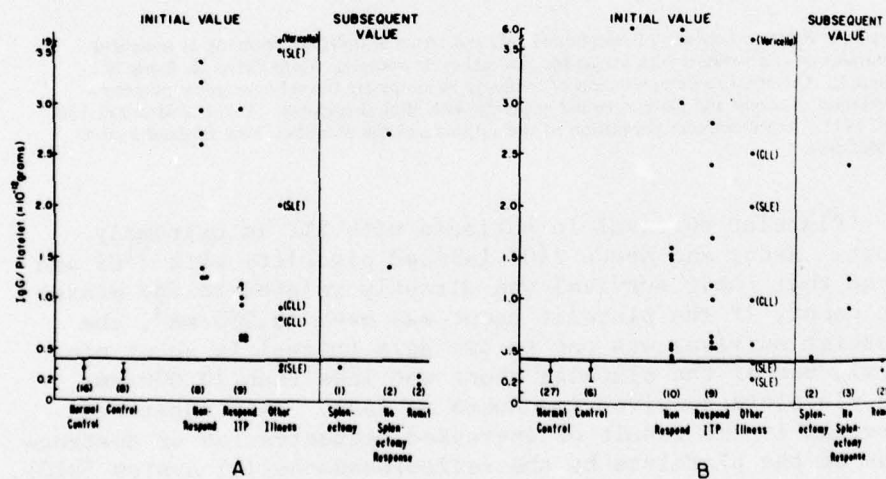


Figure 2. Range of values for surface-bound IgG (A) and serum antiplatelet antibody (B) in patients with immune thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), chronic lymphocytic leukemia (CLL), and varicella. From Dixon R, Rosse W, Egbert L: Quantitative determination of antibody in idiopathic thrombocytopenic purpura - correlation of serum and platelet bound antibody with clinical response. *N Engl J Med* 292:230-236, 1975. Reprinted with permission of the authors and the publisher, New England Journal of Medicine.

Dixon et al /9/ also found no correlation between the amount of serum antiplatelet IgG and the amount of antiplatelet IgG bound to the surface of the platelets. Even though an inverse relationship was seen between the amount of surface bound IgG and the platelet count, there was no correlation between the platelet count and the amount of serum antiplatelet antibody (Fig 3).

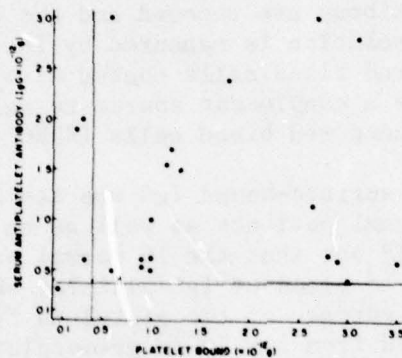


Figure 3. Relation between platelet-bound IgG and serum antiplatelet antibody as measured simultaneously in patients with idiopathic thrombocytic purpura. From Dixon R, Rosse W, Egbert L: Quantitative determination of antibody in idiopathic thrombocytopenic purpura - correlation of serum and platelet-bound antibody with clinical response. *N Engl J Med* 292:230-236, 1975. Reprinted with permission of the authors and the publisher, New England Journal of Medicine.

Platelet survival in patients with ITP is extremely short. Astor and Keene /10/ labeled platelets with <sup>51</sup>Cr and found that their survival was directly related to the platelet count; if the platelet count was over 50,000/mm<sup>3</sup>, the platelet survival was one to two days (normal is about nine days), but if the platelet count was less than 10,000/mm<sup>3</sup>, the platelets survived two hours or less. This shortened survival is the result of increased sequestration or destruction of the platelets by the reticuloendothelial system (RES). The bone marrow of such patients shows signs of increased platelet production, i.e., increased numbers of megakaryocytes, many of which show rather immature cytoplasmic differentiation, and a decrease in the number of nuclei in the megakaryocytes.



The following features are sufficient to make the diagnosis of ITP: (1) increased destruction of platelets manifested by thrombocytopenia in the presence of adequate or increased bone marrow megakaryocytes; (2) exclusion of secondary causes of thrombocytopenia such as drugs, systemic lupus erythematosus (SLE) lymphomas including chronic lymphocytic leukemia (CLL) and disseminated intravascular coagulation (DIC); (3) absence of splenomegaly (97% of patients with ITP have no splenic enlargement).

The natural history and prognosis of the disease can assume one of three forms:

*Acute ITP.* This disease is self-limiting in 80% to 90% of patients and lasts an average of five weeks, with a range of a few days to several months. About 75% of patients recover within three months. The mortality rate in this form of ITP is less than 1% and is usually caused by cerebral hemorrhage. Acute ITP occurs primarily in children, with no sex predomination. The frequency with which it follows a viral illness or a vaccination is not known, but Karpatkin and Suskind /4/ suggest the figure of 50%. Cohn /11/ retrospectively analyzed 433 Danish children less than 15 years of age with thrombocytopenia during the period 1959 to 1969 and found an incidence of 1.32/100,000 population. Table 1 shows that 52% of the cases followed an infection and that only 1.2% could be associated with a vaccination.

TABLE 1  
CAUSES OF THROMBOCYTOPENIA (433 Patients)\*

Cause	Number of patients
	(%)
Infection	225 (52)
Idiopathic	154 (36)
Vaccination (possible)	5 (1.2)
Haemolytic uraemic syndrome	4 (0.9)
Drug-induced (possible)	13 (3.0)
Food allergy (possible)	3 (0.7)
Kasabach-Merritt syndrome	2 (0.5)
Splenomegaly	1 (0.2)
Neonatal,	
drug-induced (possible) during pregnancy	7 (1.6)
infection-induced (possible) during pregnancy	1 (0.2)
idiopathic thrombocytopenia in the mother	3 (0.7)
iso-immune	1 (0.2)
Wiskott-Aldrich syndrome	8 (1.8)
Hereditary combined with immune deficiency	
(excl. Wiskott-Aldrich syndrome)	4 (0.9)
Hereditary associated with aplasia of the radii	2 (0.5)

\* From Cohn J: Thrombocytopenia in childhood: An evaluation of 433 patients, *Scand J Haematol* 16:226-240, 1976. Reprinted with permission from the author and the publisher, Munksgaard International Booksellers and Publishers, Ltd.

Table 2 illustrates the infections in these cases.

TABLE 2  
INFECTIONS CAUSING THROMBOCYTOPENIA (225 Patients)\*

Infection	Number of patients
Upper respiratory tract infection	90
Rubella	42
Tonsillitis, pharyngitis	32
Measles	14
Chickenpox	7
Infectious gastroenteritis (probable viral)	7
Mumps	5
Pneumonia	5
Pertussis	2
Scarlatina	2
Infectious mononucleosis	1
Endocarditis	1
Appendicitis ac. pur.	1
Meningitis pur. (Pfeiffer)	1
Other infections (probable viral)	15

\* From Cohn J: Thrombocytopenia in childhood: An evaluation of 433 patients. *Scand J Haematol* 16:226-240, 1976. Reprinted with permission from the author and the publisher, Munksgaard, International Booksellers and Publishers, Ltd.

Table 3 shows the most common clinical signs at diagnosis. Acute ITP is often heralded by systemic symptoms such as myalgia, headache, feverishness, and chills.

TABLE 3  
CLINICAL SIGNS AT THE TIME OF DIAGNOSIS (433 Patients)\*

Clinical signs at diagnosis	Number of patients	%
Ecchymoses	366	83
Petechiae	279	64
Epistaxis	57	13
Haematomas, subcutaneous	38	9
Mouth bleeding	29	7
Haematuria, macro- or microscopic	24	6
Gastrointestinal bleeding	22	5
Postoperative or traumatic bleeding	6	1
Menorrhagia	2	1
Intracranial haemorrhage	2	1
Retinal haemorrhage	2	1
Fever	19	4
Exanthema	15	3
Splenomegaly	14	3
Hepatomegaly	10	2
Lymph node enlargement	7	2

\* From Cohn J: Thrombocytopenia in childhood: An evaluation of 433 patients. *Scand J Haematol* 16:226-240, 1976. Reprinted with permission from the author and the publisher, Munksgaard, International Booksellers and Publishers, Ltd.

*Chronic ITP.* This form of ITP is most often found in adults, and can last from several to 20 or more years. The female/male ratio is 3/1. Platelet count is usually in the range of  $30,000/\text{mm}^3$  to  $60,000/\text{mm}^3$ , although counts of less than  $10,000/\text{mm}^3$  are seen. A predisposing illness is rarely discerned in this variety.

*Intermittent type.* In this form, there are repetitive bouts of thrombocytopenia each lasting less than six months, with a return to normal platelet count between episodes. /12/ This pattern of exacerbations and remissions (each remission lasts at least three months) may go on for years; in fact, Damashek et al /13/ report that as many as five bouts have occurred in patients over a four to 18 year interval.

The therapy of ITP serves only to control the severity of the disease until such time as the disease remits. With this in mind, it is clear that the zealous urge to overtreat the patient must be subdued, especially in children who have a high incidence of spontaneous remissions. Three avenues of therapy are available: (1) steroids; (2) splenectomy; and (3) immunosuppressive drugs.

*Steroids.* The major action of steroids appears to be reduction in the sequestration of the platelets by the RES. Fig 4 shows the effects of ITP serum on platelet counts of normal volunteers pretreated with prednisone. The drug is capable of significantly decreasing the thrombocytopenic effect of this serum. When treating patients for ITP with prednisone, 1 mg/kg/day, as many as 80% show a favorable response with a return of the platelet count to normal in 15% to 60% of cases; the percentage of patients who show a sustained normalization of the platelet count is considerably less. Response to prednisone usually occurs within a few days, but may take one to two months. If the patient does not respond, an increase in dose to 100 mg/kg/day may lead to a further rise in the platelet count. A platelet count of over  $50,000/\text{mm}^3$  is unnecessary, because spontaneous bleeding does not occur above this level. Most physicians treat patients for about four to six weeks and then taper the steroid gradually over a period of several months. If the platelet count falls during the tapering period to the  $20,000/\text{mm}^3$  to  $30,000/\text{mm}^3$  range, most physicians recommend splenectomy after boosting the steroid to 100 mg/kg/day for four to five days.



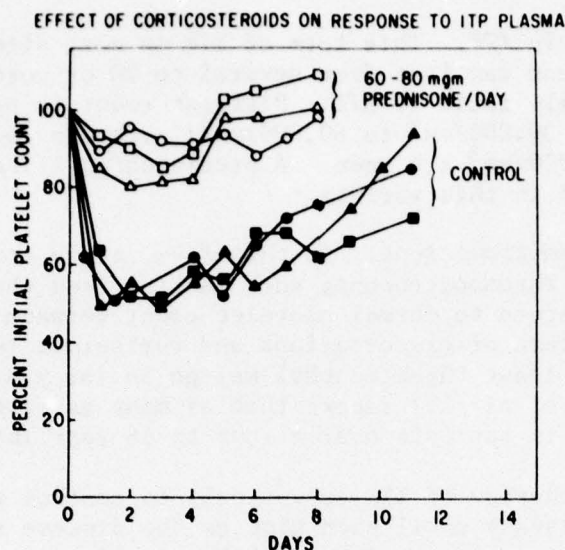


Figure 4. Effects of prednisone on the response to idiopathic thrombocytopenic purpura (ITP) plasma. Results of giving three normal individuals ITP plasma are shown by the solid symbols. The open symbols show results of giving the same dose of ITP plasma to the same individuals during administration of 60 to 80 mgm of prednisone per day. In the different recipients, prednisone was started 3 hours, 1 day, and 3 days prior to infusing ITP plasma and in each instance was continued for a minimum of 7 days. The control infusions in two instances were given 1 and 2 months prior to the infusions with prednisone, and in one instance three weeks after the infusion with prednisone. From Shulman NR, Marder VJ, Weinrach RS: Comparison of immunologic and idiopathic thrombocytopenia. *Trans Assoc Am Physicians* 77:65-78, 1974. Reprinted with permission of the authors and the publisher, William J. Dornan, Inc.

Many physicians do not administer steroids to children with acute ITP because the mortality rate is so low. McClure /14/ found that although treatment produced a transient rise in the platelet count, the steroids did not affect the duration of the disease in children. Benham and Taft /15/ and Lammi and Lovric /16/ similarly concluded that steroids seem to help control bleeding initially, but that there is no significant difference in long-term remission rate or time to remission in treated versus untreated patients. Dixon et al /9/ found an inverse correlation between the amount of surface bound IgG on the platelets at the time of diagnosis and the response to therapy. All responders to prednisone showed a decrease in platelet bound IgG to normal levels as the platelet count rose. Patients who did not respond to prednisone showed continued high levels of surface bound IgG. They also found that those

patients had the highest initial values of platelet bound IgG: 7/8 with levels of platelet bound IgG greater than  $11 \times 10^{-13}$  grams/platelet failed to respond to prednisone, whereas all patients with  $5-10 \times 10^{-13}$  grams/platelet of IgG responded. Serum levels of IgG antiplatelet antibodies did not correlate with response to prednisone or the platelet counts. In this study, patients with chronic ITP showed only a 30% response to steroids, which is somewhat lower than reported by others.

*Splenectomy.* Since the RES is probably a major site of removal of IgG coated platelets, splenectomy has received wide attention as therapy in ITP. Fig 5 shows that various doses of ITP plasma infused into a splenectomized volunteer caused much less thrombocytopenia than when infused into a nonsplenectomized normal individual.

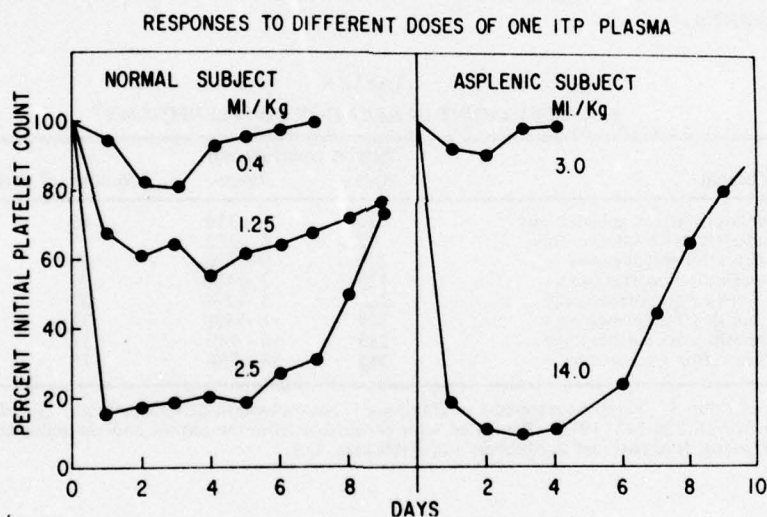


Figure 5. Comparison of response of normal and splenectomized persons to idiopathic thrombocytopenic purpura (ITP) factor. The graph on the right shows the effects of the same ITP plasma in a splenectomized person. Note that the ITP plasma dose which did not produce thrombocytopenia in the splenectomized person was greater than the dose which produced marked thrombocytopenia in the normal individual. From Shulman NR, Marder VJ, Weinrach RS: Comparison of immunologic and idiopathic thrombocytopenia. *Trans Assoc Am Physicians* 77:65-78, 1974. Reprinted with permission from the authors and the publisher, William J. Dornan, Inc.

Overall, about 80% to 90% of patients with acute ITP respond to splenectomy with a rise in platelet count to normal, compared to about 50% of patients with chronic ITP; however, 10% of these responders relapse, usually within one year. The response is not predicted by the duration of disease

prior to splenectomy or by a prior response or lack of response to antecedent steroid therapy. Harrington and Arimura /17/ reported a 100% response to splenectomy in patients who had responded to steroids, but the duration of response was not reported. Age is an important factor in response; Harrington and Arimura /17/ found an 88% response rate in patients under 45 years of age compared to a 60% response rate in those over 45 years of age. In acute ITP in children, splenectomy is contraindicated early in the course and should be considered only for children in whom the disease persists long enough to approach the criteria for chronic ITP. In Cohn's series /11/, 46 of 433 children with ITP underwent splenectomy at a median of six months after diagnosis (with a range of one to 87 months). Table 4 shows the pre- and postsplenectomy platelet counts in these patients; 12/46 (26%) relapsed after splenectomy, and 3/46 had several relapses.

TABLE 4  
PLATELET COUNT IN RELATION TO SPLENECTOMY \*

Time period	Platelet count (mia/l)		Number of patients
	Mean	Range	
Immediately before splenectomy	73	1 - 336	45
Immediately after splenectomy	92	1 - 322	7
One day after splenectomy	244	2 - 770	29
One week after splenectomy	439	3 - 1488	39
Two weeks after splenectomy	380	3 - 1270	29
One month after splenectomy	349	1 - 1480	31
Six months after splenectomy	255	16 - 960	21
One year after splenectomy	244	35 - 704	15

\* From Cohn J: Thrombocytopenia in childhood: An evaluation of 433 patients. *Scand J Haematol* 16:226-240, 1976. Reprinted with permission from the author and the publisher, Munksgaard, International Booksellers and Publishers, Ltd.

The indications for splenectomy are: (1) duration of disease greater than three months in both adults and children; (2) relapse of disease following attempted steroid tapering; (3) patient unreliability in taking prescribed medications; and (4) no assurance of follow-up. Some authors have advocated splenectomy at the onset of disease in adults because they seldom have acute ITP and infrequently manifest a prolonged response to steroids. Contraindications to splenectomy include pregnancy and other medical problems that would contraindicate surgery, and an age of less than two years.



In an attempt to improve the ability to predict response to splenectomy, Najean /18/ in 1967 labeled platelets with  $^{51}\text{Cr}$  and found that 61% of his patients had a "splenic" pattern of sequestration. The other 39% showed either an "hepatic" or a "spleno-hepatic" pattern. As can be seen in Table 5, he found that of the patients with a predominantly splenic pattern who were followed for one year after splenectomy, 92% had a rise of platelet counts to greater than  $80,000/\text{mm}^3$  at one year of follow-up. He also found that 70% of these patients had platelet counts of greater than  $200,000/\text{mm}^3$ , whereas of those with the "predominantly hepatic" pattern, only 33% had platelet counts of at least  $80,000/\text{mm}^3$  at one year of follow-up and 11% had platelet counts of at least  $200,000/\text{mm}^3$ . Patients who relapsed after a splenectomy developed the "hepatic" pattern of sequestration, but repeat  $^{51}\text{Cr}$  scans were not done on all patients who did not relapse.

TABLE 5

IMMEDIATE PLATELET RISE AFTER SPLENECTOMY (5TH-10TH DAY) (MEAN VALUES)\*

Site of platelet destruction	No. of patients	Platelet count (thousands/cu.mm.)
Predominantly hepatic	10	165
Hepato-splenic	23	425
Predominantly splenic	80	820
Total	113	

(b) PLATELET COUNT 3-6 MONTHS AFTER SPLENECTOMY

Site of platelet sequestration	Platelet count (thousands/cu.mm.)		
	More than 200	80-200	Less than 80
Predominantly hepatic	1	2	7
Hepato-splenic	8	9	4
Predominantly splenic	54	16	6

(c) PLATELET COUNT MORE THAN 1 YEAR AFTER SPLENECTOMY

Site of platelet sequestration	Platelet count (thousands/cu.mm.)		
	More than 200	80-200	Less than 80
Predominantly hepatic	1	2	6
Hepato-splenic	3	8	5
Predominantly splenic	36	12	4

\* From Najean Y, Ardaillou N, Dresch C, et al: The platelet destruction site in thrombocytopenic purpura. *Br J Haematol* 13:409-426, 1967. Reprinted with permission from the authors and the publisher, Blackwell Scientific Publications, Ltd.

Table 6 shows that age played an important role in the findings in this study: 48% of patients over 50 years of age had the "hepatic" pattern and 35% showed the "splenic" or "spleno-hepatic" patterns, whereas 81% of patients under age 15 had either the "exclusively splenic" or "predominantly splenic" patterns.

TABLE 6  
CORRELATION BETWEEN THE SITE OF PLATELET SEQUESTRATION AND PATIENT AGE IN 288 CASES OF ACTIVE ITP \*

Apparent site of sequestration	Age of the patients in years					Total
	Under 5	5-15	15-30	30-50	Over 50	
	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	
Exclusively hepatic	—	1 (0.8)	1 (2.1)	2 (3.9)	10 (21.7)	14 (4.9)
Predominantly hepatic	—	3 (2.9)	5 (10.4)	8 (15.7)	12 (26.1)	28 (9.7)
Hepato-splenic	9 (26)	17 (15.8)	16 (33.4)	21 (41.2)	8 (17.4)	71 (24.6)
Predominantly splenic	13 (37)	30 (27.7)	14 (29.1)	8 (15.7)	11 (23.9)	76 (26.4)
Exclusively splenic	13 (37)	57 (52.8)	12 (25)	12 (23.5)	5 (10.9)	99 (34.4)
Total	35	108	48	51	46	288

\* From Najean Y, Ardaillou N, Dresch C, et al: The platelet destruction site in thrombocytopenic purpura. *Br J Haematol* 13:409-426, 1967. Reprinted with permission from the authors and the publisher, Blackwell Scientific Publications, Ltd.

Shulman /3/, Baldini /19, and Aster and Jandl /20/ found the site of sequestration of platelets in ITP to be correlated with the amount of serum antiplatelet antibody in that relatively low concentrations of antibody were associated with splenic sequestration, and relatively high concentrations led to hepatic sequestration. Dixon et al /9/ also found that those patients who failed to respond to splenectomy had the highest amount of platelet bound IgG at diagnosis. This fact correlates with the findings of Najean et al /18/ who showed that steroid response was seen only in patients with the "exclusively" or "predominantly" splenic sequestration patterns (Table 7).

TABLE 7  
Correlation Between the Site of the Platelet Sequestration and the Effectiveness of Steroid Therapy Before or After the Isotopic Investigation (Dose Schedule: Prednisone, 1 mg/kg/day) \*

Apparent site of sequestration	Effectiveness of steroid therapy	
	No improvement	Effective (platelets more than 100,000/cu.mm.)
	Cases (% of total)	Cases (% of total)
Exclusively or predominantly hepatic	26 (25)	6 (6.5)
Hepato-splenic	29 (27.5)	16 (18)
Exclusively or predominantly splenic	50 (47.5)	68 (75.5)
Total	105	90

\* From Najean Y, Ardaillou N, Dresch C, et al: The platelet destruction site in thrombocytopenic purpura. *Br J Haematol* 13:409-426, 1967. Reprinted with permission from the authors and the publisher, Blackwell Scientific Publications, Ltd.

Idiopathic thrombocytopenic purpura in the pregnant woman is a difficult problem to manage because there is a twofold increase of spontaneous abortion, an increase in intrapartum and postpartum hemorrhage, and neonatal thrombocytopenia from placental transfer of the IgG<sub>3</sub> antiplatelet antibodies which increases the danger of intracranial bleeding in the fetus during parturition. Maternal mortality is low, however. Treatment is usually with steroids, especially if the patient is more than 20 to 30 weeks pregnant, when the risk of the steroids to the developing fetus is lessened. Splenectomy in the pregnant patient is much more dangerous both to the mother and the fetus.

*Immunosuppressive drugs.* Cytosan<sup>®</sup>, Imuran<sup>®</sup>, 6MP, 6TG, MTX, and others have been tried in small numbers of patients with ITP with moderate success, but their use remains experimental.

#### Platelet Autoantibodies In Other Clinical Disorders

Autoantibodies also occur in Evans' syndrome of autoimmune hemolytic anemia and autoimmune thrombocytopenia which has no known etiology: CLL and other lymphomas (primarily non-Hodgkin's lymphomas); collagen vascular diseases, especially SLE and rheumatoid arthritis (RA); hyperthyroidism; and perhaps others, including at least one case of autoimmune thrombocytopenia and Hashimoto's thyroiditis. /21/ In SLE, autoimmune thrombocytopenia, autoimmune hemolytic anemia and, less commonly, autoimmune neutropenia, may precede other manifestations of lupus by several years. Eighty per cent of SLE patients have serum antiplatelet antibodies, but few of these patients manifest thrombocytopenia. Autoimmune hemolytic anemia in CLL is much more common than autoimmune thrombocytopenia and even though both occur more commonly with advanced disease, their presence or severity does not correlate with control of the white blood cell count.

Post transfusion purpura is a rare disorder (about 16 cases reported) in which the blood recipient develops thrombocytopenia about one week after transfusion. All recipients documented to date with this syndrome except one had platelets which were negative for the platelet antigen P1A1, yet their plasma antibodies reacted with the P1A1 antigen. It is believed that in these cases transfusion



of incompatible platelets leads to the formation of isoantibodies by the recipient; however, the platelet destruction could be on an "innocent bystander" basis due to the deposition of AgAb complexes on the recipient's platelets. One such patient with two separate antiplatelet antibodies was successfully treated with plasmapheresis on three successive days. /22/ Isoantibodies to platelets can lead to congenital thrombocytopenia. Maternal exposure to the infant's incompatible platelets may result in the production of IgG antibodies by the mother; these antibodies then cross the placenta and react with the fetal platelets. Fetal platelet antigens that have led to this problem are P1A1, P1Grly<sup>b1</sup>, and P1Grly<sup>c1</sup>. Fortunately, fetal bleeding and thrombocytopenia are uncommon in this situation.

Congenital thrombocytopenia of nonimmune nature also occurs in certain infections such as rubella, toxoplasmosis, cytomegalovirus, herpes simplex, and syphilis, as well as in DIC, malignancies, and various drug-induced thrombocytopenias. Thrombocytopenia also occurs in certain allergic reactions such as insect bites, tetanus antitoxin immunizations, and other inoculations. These cases may be caused by AgAb complexes.

#### **Drug-Induced Thrombocytopenia**

A number of drugs cause thrombocytopenia by an immune mechanism leading to increased destruction of the antibody-coated platelets by the RES or by AgAb complexes which fix complement. Antiplatelet antibodies caused by drugs are almost always IgG, although in the case of hydrochlorothiazide and rifampin, the antibody has been IgM. Most drugs act as haptens which attach to the platelet membrane, thus forming the "antigen" to which the antibody is directed, with platelet destruction ensuing. In some cases, the drug acts as a hapten which combines with a plasma protein to form the antigen that stimulates antibody production. The AgAb complex so formed then precipitates on the platelet membranes, complement is fixed at the site, and platelet destruction rapidly follows. Complement may or may not be involved; if uninvolved, only platelet agglutination occurs, leading to RES sequestration (primarily in the spleen) followed by destruction of the coated platelet by the splenic macrophages.

*Present Concepts, Hematology-Oncology Symposium, Winter 1977-1978*

Sedormid is the first drug to be described as causing immune thrombocytopenia. Ackroyd /23/ in 1949 transfused serum from a thrombocytopenic patient taking this drug into a normal recipient and caused thrombocytopenia in that recipient. Complement fixation was involved in the process. In the absence of the drug, thrombocytopenia did not occur. Drugs which have been associated with immune thrombocytopenia may be placed into the following categories:

1. *Cardiac drugs.* Severe thrombocytopenia (less than 5,000/mm<sup>3</sup>) can occur within 12 hours of ingestion of quinine and quinidine in patients previously sensitized to them. The duration of the severe thrombocytopenia is usually less than two days, followed by a prompt recovery to normal platelet counts in about one week. The patients may note a prodrome of feverishness, chills, malaise, lethargy, and pruritus. Mucosal hemorrhages are common and petechiae on the palate and dependent areas are universal. The amount of drug necessary to produce this problem may be small: one tablet will suffice. Patients with this problem should be warned not to take any compound containing quinine, including tonic water. Other cardiac drugs associated with immune thrombocytopenia include digitoxin, hydrochlorothiazide, Aldomet®, Diamox®, and Dilantin®.

2. *Tranquilizers and antidepressants:* Meprobamate and carbamazepine (Tegretol®).

3. *Antibacterials:* Sulfonamides (sulfathiazole and sulfamethazine), rifampin, penicillin and analogues (carbenicillin and ticarcillin), and para-aminosalicylic acid.

4. *Miscellaneous:*

a. Heparin. There is evidence for an immune etiology in some cases of thrombocytopenia in patients receiving this drug. Babcock et al /24/ reported five patients who developed marked thrombocytopenia while on heparin therapy (given every four hours intravenously). They found that the serum of these patients induced normal platelets to aggregate if serum was collected during the period of maximum thrombocytopenia; if collected one to ten days after discontinuance of heparin, it had no effect on platelet aggregation. Heparin alone did not lead to platelet aggregation. Using the platelet factor III (PF-3) availability assay for the presence of antiplatelet

antibodies, Babcock et al /24/ found that adding heparin to normal platelet rich plasma plus the globulin fraction proteins from the patients' serum significantly shortened clotting times in four of the five patients. Absorption of the globulin fractions from the plasma of these patients with rabbit-antihuman IgG resulted in no shortening of the clotting times. Thus, though no serum antibodies were detected with this technique in the absence of heparin, the presence of IgG from the patients and heparin led to increased PF-3 availability. When protamine was added to the system with the heparin, shortening of the clotting time did not occur. Platelet transfusions in these thrombocytopenic patients led to no increment in the platelet counts. More sensitive assays for antiplatelet antibodies bound to the platelet surface in such patients might be directly indicative of an immune-mediated process.

b. Gold. Isolated cases of thrombocytopenia with gold therapy appear to be caused by immune destruction; in these cases, the bone marrow contains increased or normal numbers of megakaryocytes. Two studies /25,26/ reported a shortened survival of  $^{51}\text{Cr}$  tagged platelets in this setting. Levin et al /27/ reported a patient with anemia and thrombocytopenia who received gold therapy (total dose 217 mg of elemental gold) for RA. After discontinuing the gold, the anemia resolved, but the thrombocytopenia continued for the next four months and did not respond to dimercaptol. (Unfortunately, gold excretion was not measured, and this therapy may have been insufficient.) Immediately following splenectomy, the platelet count rose from 2,000/mm<sup>3</sup> to 54,000/mm<sup>3</sup>, and to normal over the ensuing three months. The platelet half-life by the  $^{51}\text{Cr}$  method prior to splenectomy was 9.6 hours. The authors looked for antiplatelet antibodies in the serum by using a complement fixation test, a PF-3 release assay, and by the inhibition of clot retraction in the presence of various concentrations of gold. They found no evidence of serum antibodies; however, gold concentration in excess of 20  $\mu\text{g/ml}$  in serum-free experiments led to complement fixation; also, PF-3 release was markedly prolonged in the presence of gold concentrations greater than 1,500  $\mu\text{g/ml}$ . They also found histological evidence of platelet phagocytosis by the splenic macrophages. A further indication of the role of the spleen was the finding that the splenic leukocytes produced about 60 times more



IgG than did the spleens of 10 normal patients and six times the amount produced by the spleens of 15 patients with ITP. Unfortunately, Levin et al /27/ did not compare the splenic IgG production of their patient to other patients with RA of the same degree of severity. At least some of this antibody binds both to intact platelets and to platelet membranes; this attachment is not dependent on the presence of gold. This patient's peripheral blood lymphocytes underwent significant blastogenic transformation (as measured by the <sup>3</sup>H-thymidine uptake method) when exposed to aurothiomalate in 25 to 50 µg/ml concentrations, also implying a cell-mediated immunity. Three normal patients and two patients with RA in whom gold had not been used for more than six months showed no such lymphocyte transformation in the presence of gold. Thus, lymphocyte transformation in the presence of gold, increased production of antiplatelet antibodies by the spleen, and a shortened platelet half-life imply a significant, if not etiologic, role for the thrombocytopenia in this patient.

#### Non-Immune Thrombocytopenia

1. *Disseminated intravascular coagulation.* Disseminated intravascular coagulation, sometimes referred to as consumptive coagulopathy, is a term applied to a number of clinical and pathophysiological states in which for one reason or another the coagulation cascade results in deposition of fibrin within the vascular tree. In the acute situation, this is accompanied by:

- Platelet consumption, leading to thrombocytopenia
- Consumption of coagulation factors I, V, and VIII
- Production of soluble fibrin by the action of thrombin on fibrinogen
- Production of fibrin (and fibrinogen) degradation products (FDPs) by the action of plasmin (a potent peptidase) on both fibrin and fibrinogen, as well as on several other peptide hormones including adrenocorticotrophic hormone (ACTH), glucagon, and somatotropin

- Red blood cell fragmentation (schistocytes or helmet cells) which is usually, but not always, present on the peripheral blood smear.
- Depletion of naturally occurring antithrombins, such as "antithrombin III" which serve as brakes on the coagulation cascade by removing the activated factors and thrombin.

Thus, in the situation of acute DIC the laboratory evaluation would result in the following findings:

- Thrombocytopenia is usually moderate, with a platelet count of  $40,000/\text{mm}^3$  to  $60,000/\text{mm}^3$  but may be as low as  $10,000/\text{mm}^3$  to  $20,000/\text{mm}^3$ .
- Anemia usually occurs with schistocytes on the peripheral smear.
- Prolonged partial thromboplastin time (PTT) is caused by depletion of coagulation factors by accelerated consumption via the coagulation cascade, by destruction by plasmin, and by the interference in the interaction of the coagulation factors by FDPs. Such interference prevents the normal action of thrombin on fibrinogen and on polymerization of fibrin monomer molecules to form soluble fibrin strands. In addition, FDPs interfere with other coagulation factors.
- Prolonged prothrombin time (PT) occurs for the same reasons as for the prolongation of the PTT because factors I, II, V, and X are in the "final common pathway" of coagulation. The only coagulation factor measured by the PT (the "extrinsic" pathway) and not by the PTT (the "intrinsic" pathway) is factor VII which is rarely consumed in DIC (except perhaps in the DIC caused by meningococcemia).
- Prolonged thrombin time (TT). This test measures the rate of conversion of the patient's fibrinogen to fibrin clot by exogenously added thrombin,

thereby bypassing the coagulation cascade above the level of the production of thrombin and will be abnormal only if there is:

- Hypofibrinogenemia (below 75 mg%)
- One of the rare abnormal fibrinogenemias (dysfibrinogenemias)
- Some circulating antithrombin such as heparin or FDPs
- Excessive plasmin which partially digests the fibrinogen molecule so that thrombin cannot have its specific peptidase action (cleavage of the fibrinopeptides A and B from fibrinogen)

In acute DIC all of these except the second one apply.

- Hypofibrinogenemia is quantitated in a rather crude manner in most laboratories by heating plasma which precipitates the fibrinogen in a capillary tube. The height of the precipitate is measured after centrifugation for three minutes. The number is located on a conversion table and the fibrinogen level is thus obtained. Normal plasma fibrinogen level is 250 to 350 mg%, but it is elevated in many inflammatory diseases and in chronic liver diseases, especially Laennec's cirrhosis. A normal or mildly low fibrinogen level under these conditions might represent considerable fibrinogen consumption.
- The measurement of FP-A and FP-B by RIA may offer more clearcut proof of the presence of thrombin in the system, i.e., DIC. Fig. 6 illustrates the relative rates of cleavage of these two fibrinopeptides by thrombin and plasmin. As can be seen in the figure, plasmin causes no cleavage of FP-A, whereas thrombin cleaves both, but its action in cleaving the A peptide is much faster than its ability to split off the B peptide. /28/ Markedly elevated levels (greater than 7 pmoles/ml) of FP-A have been seen in patients



with acute pulmonary embolism, acute thrombophlebitis, and DIC (normal levels are less than 1.5 pmoles/ml) within hours to days of the onset of the condition. Moderately elevated levels of 1.5 to 7 pmoles/ml were seen in those conditions in a subacute phase, and also in cases of septicemia, pneumonia, cellulitis, carcinomatosis (without evidence of thrombosis), SLE, renal transplant rejection, and aortic aneurism. /29/

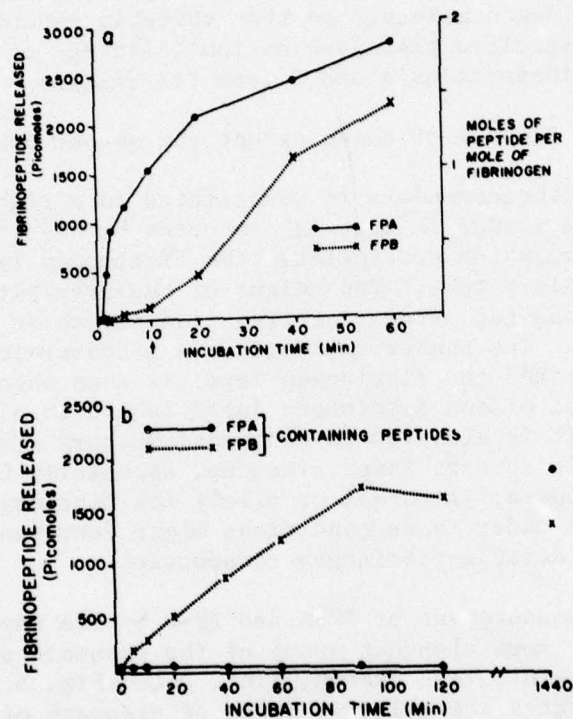


Figure 6. Cleavage of fibrinopeptide A (FPA) and fibrinopeptide B (FPB) by thrombin (in a) and by plasmin (in b). From Nossel HL: Radioimmunoassay of fibrinopeptides in relation to intravascular coagulation and thrombosis. *N Engl J Med* 295:428-432, 1976. Reprinted with permission of the author and the publisher, New England Journal of Medicine.

Activated factors produced in the course of activation of the coagulation cascade serve to perpetuate the clotting unless removed from the circulation. Removal can occur in several ways. Two important ones are removal by the RES and inactivation by AT-III: an alpha-2 macroglobulin of 62,300 molecular weight that is responsible for the inactivation of activated factors X, XI, XII, IX as well as of thrombin, plasmin, and perhaps factor VII. All activated factors are proteases with a serine moiety at the "business end" of the molecule. An arginine receptor site on the AT-III molecule interacts with this serine residue, thus inactivating the proteases. In DIC, all patients have elevated plasma levels of fibrinopeptide A, but the degree of elevation does not correlate with the degree of hypofibrinogenemia. Because endotoxin is known to cause RES blockade, it will, in addition to initiating DIC, also prevent adequate removal of the activated coagulation factors formed, thereby intensifying the clotting. Antithrombin III eventually becomes depleted in the presence of a DIC, often to levels of less than 10% of normal. The half-lives of the activated factors and thrombin then begin to lengthen, allowing more factor consumption. Fig. 7 shows the effects of heparin infusion of FP-A levels in patients with various disorders: in acute thromboembolism, the FP-A levels returned to normal within 15 minutes of infusion but in patients with thrombotic thrombocytopenic purpura (TTP), lobar pneumonia, and other conditions, heparin did not lower the FP-A level. Fig. 8 shows that the inhibition of thrombin by AT-III is greatly enhanced by the presence of heparin. /30/ Fig. 9 shows the same phenomenon with plasmin. Apparently the combination of the serine protease and AT-III is necessary to expose a lysine receptor site for heparin which is *inactive* when present by itself. The combined heparin AT-III complex then significantly accelerates inactivation of the protease.

In contrast to acute DIC which is clinically manifested by intravascular clotting, purpura, and bleeding from mucosal sites and intravenous puncture sites, there are conditions such as prostatic carcinoma, lung cancer, and adenocarcinomas of the gastrointestinal tract and genitourinary tract in which a chronic, long-term DIC is present. This chronic DIC is usually manifested by thrombosis (including migratory thrombophlebitis) and major vessel thrombosis (including the pulmonary vasculature). The consumption

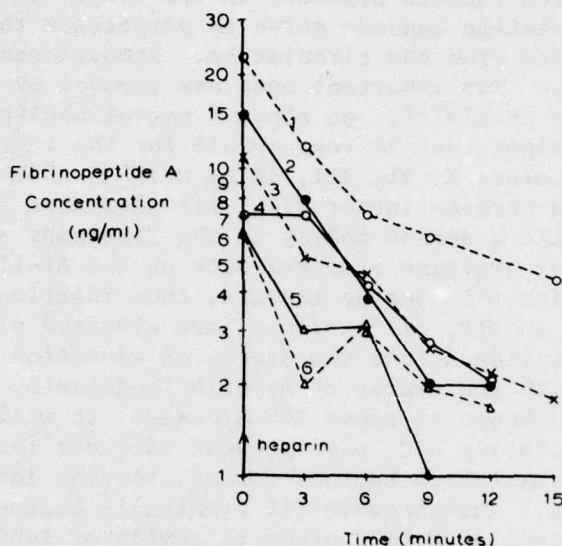


Figure 7. Effect of heparin infusion (10,000 U) in six patients with elevated fibrinopeptide - A levels before infusion. From Nossel HL: Radioimmunoassay of fibrinopeptides in relation to intravascular coagulation and thrombosis. *N Engl J Med* 295: 428-432, 1976. Reprinted with permission of the author and the publisher, New England Journal of Medicine.

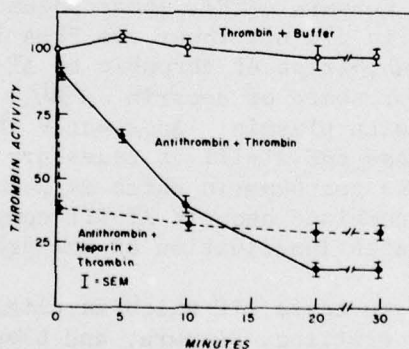


Figure 8. Inhibition of thrombin by antithrombin in the presence and absence of heparin. Thrombin activity is expressed as percentage of the control value. From Rosenberg RD: Actions and interactions of antithrombin and heparin. *N Engl J Med* 292:146-151, 1975. Reprinted with permission of the author and the publisher, New England Journal of Medicine.



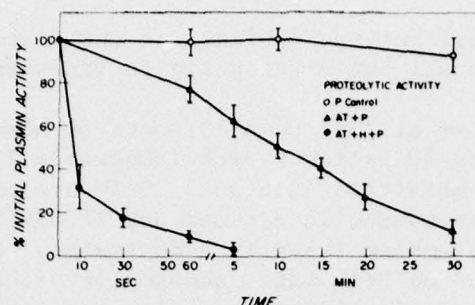


Figure 9. Proteolytic activity ( $\pm$ SEM) of plasmin (P), antithrombin (AT) with plasmin, and antithrombin, heparin (H) and plasmin. From Rosenberg RD: Actions and interactions of antithrombin and heparin. *N Engl J Med* 292:146-151, 1975. Reprinted with permission of the author and the publisher, New England Journal of Medicine.

of platelets and coagulation factors in these conditions may be slow enough to be compensated by increased synthesis, and, instead of a prolonged PTT, one may find a shortened one because of activated coagulation factors already present in the plasma. Sun et al /31/ studied 61 patients with various types of malignancies by means of a coagulation profile including PT, PTT, ethanol gelation test (similar to the 3P test for fibrin monomer), FDP level, and platelet count and found that only three patients were normal in all these respects. Carcinoma of the bladder was the most common tumor in the series (22 patients). Patients were selected for study if they had a history of unusual bleeding or bruising: 56% had a recent bleeding episode, 20% had a recent episode of thrombophlebitis or thromboembolism, and 9% had a pulmonary embolism. The authors found that: (a) five patients had seven coagulation abnormalities each; (b) 34 patients had three to five abnormalities each, including 27 with elevated FDPs, 20 with prolongation of PT, 20 with elevated fibrinogen levels, 16 with a positive ethanol gelation test, eight with a prolonged PTT, eight with thrombocytopenia, and two with thrombocytosis; (c) hypofibrinogenemia was uncommon, occurring in six patients, of whom five had metastatic disease; (d) the only significant differences between patients with metastatic and non-metastatic disease were the incidences of prolonged PT and elevated FDPs; (e) specific coagulation factor assays were performed in 15 patients. The factor VIII level was normal or

increased in all but one patient and the factor V levels were normal in all but a few patients (in whom it was low).

Hagedorn et al /32/ used 13 tests of hemostasis and fibrinolysis on 50 patients with inoperable lung cancer of whom half had metastatic disease. Only one patient had a history of thromboembolic disease and 11 patients had a history of some bleeding (usually hemoptysis). Only two of the 50 patients had no hemostatic abnormality (the average was 3.5 abnormal tests per patient). An elevated fibrinogen level was the most common abnormality, occurring in 82% of patients; no patient showed hypofibrinogenemia. Prothrombin times were moderately prolonged in 58% of patients and shortened in only two patients. The following tests were abnormal in less than 50% of the patients:

- Platelets - 30% had elevated platelet counts and 4% had low platelet counts.
- Partial thromboplastin time - 20% had a shortened PTT, and none had a prolonged PTT.
- Thrombin time - 13% had a prolonged TT and two patients had a shortened TT.
- Fibrin degradation products - 38% showed an increased level.
- Ethanol gelation test - 11% had an abnormal positive test.

In these patients, evidence of DIC in the classical sense was uncommon, but there was a relatively high incidence of hemostatic abnormalities. While the number of cancers evaluated and the number of patients in each category /31,32/ was small, the concept of "hypercoagulability" on the basis of a compensated DIC in cancer patients is probably valid. More rigorous stratification of such patients into stage of disease, presence of concomitant chemotherapy or radiotherapy, and the presence of concomitant disorders such as infection and shock should be done. The association of acute or subacute DIC in acute leukemia without the presence of infection is well documented, especially in the promyelocytic variety.



Mertens et al /33/ found that of 19 patients with benign prostate hypertrophy, five had slightly elevated FDPs (the mean was 8  $\mu\text{gm/ml}$ ), but that of 17 patients with prostatic cancer (all stages) the FDPs were elevated in 11, nine of whom had significantly elevated values. The degree of elevation of the FDPs correlated roughly with the grade of the tumor, and was highest in the most anaplastic tumors. These authors also tested 25 patients preoperatively with the ethanol gelation test and found significantly more abnormalities (of at least a 2+ degree of positivity) in those patients with malignant disease (a 40% incidence of a 2+ or greater test) than in those with benign disease (an 8% incidence of a 2+ or greater test). These tests point to an evolving process of fibrin monomer production and fibrinogen/fibrin proteolysis by plasmin. All patients with an abnormal ethanol gelation test (1 to 2+ positive) bled excessively at surgery, whereas none of the patients with a normal ethanol gelation test did so.

The FDPs in these patients with cancer may be caused by the production of tissue proteases. Reich /34/ showed that cultured malignant cells produced plasminogen activators that can act directly to activate the proteolytic system without going through the normal mechanism of activated factor XII (Hageman factor) as occurs in "secondary fibrinolysis."

The disorders grouped under the term "DIC" clearly represent a spectrum of degrees of fibrinogen consumption, factor consumption, platelet consumption, and anemia. No laboratory results other than shortened platelet survival, increased fibrinogen turnover, and perhaps shortened RBC survival will invariably be abnormal in these syndromes. The problem is that each hemostatic element is in a dynamic state which depends on the rate of production and the rate of consumption. The diagnosis of DIC is dependent on the clinical setting, the underlying disease process, and appropriate abnormal laboratory tests.

I will not deal with therapy other than to stress that the underlying disease must be controlled; if this is done, no specific therapy is necessary because the normal homeostatic processes of the body will rapidly restore the normal balance. Heparin therapy by continuous infusion along with a source of AT-III such as fresh frozen plasma (FFP) may be



indicated in certain circumstances in which bleeding is brisk. Therapy should include FFP (which replaces all coagulation factors), cryoprecipitate (high in factors I, VIII, and XIII), and, most important, platelet concentrates. Rake et al /35/ treated four patients, three with fulminant hepatic failure and one with a severe relapse of serum hepatitis, with continuous infusion heparin and FFP. All four patients showed evidence of DIC as manifested by prolongation of the PT, hypofibrinogenemia, and elevated serum FDPs. All patients showed rapid correction of their hemostatic abnormalities, and all recovered after treatment for a period of 12 to 20 days. While the role played by the controlling DIC is uncertain in these patients, it did allow them to recover before complications occurred.

Heparin itself has been associated with mild thrombocytopenia when used in cases of pulmonary embolism and thrombophlebitis. The mechanism in some cases has apparently been DIC. /36,37/ Bell et al /37/ studied 52 patients on heparin therapy. Prior to heparin infusion, which was given for a minimum of five days, the patients' hematocrits, white cell blood counts, peripheral smears, Lee-White clotting times, PTs, PTTs, and fibrinogen levels were measured. Throughout heparin therapy, platelet counts were measured every other day until cessation of therapy or until the platelet count returned to normal following therapy. Heparin effect was measured with the Lee-White clotting time; the other tests were repeated at five to seven day intervals. Sixteen patients developed thrombocytopenia during heparin therapy (platelet count less than  $100,000/\text{mm}^3$ ) which began on day two and reached a nadir at days three or four. In 10 of these 16 patients, elevated FDPs were seen concomitantly, and five of these 10 also had a decrease in fibrinogen levels (three had a decrease of 50% from the initial value and two had a 75% decrease), but the fibrinogen decreased to less than 100 mg% in only one patient. Discontinuation of heparin in these 16 patients led to a return of platelet counts to normal within three to five days. At no time were schistocytes seen on the peripheral smear. Two of the thrombocytopenic patients had excessive bleeding from venipuncture sites; they also had increased FDPs and decreased fibrinogen levels. Of the nonthrombocytopenic patients, three had mild elevation of FDPs and one had a decrease in fibrinogen levels from preheparin levels. The PT was normal except for two patients who also had marked elevation of FDPs, thrombocytopenia,

and PTTs of greater than three minutes; all other patients had PTTs of two to three minutes. Thrombocytopenia did not correlate with the dose or the lot number of heparin used. This evidence suggests that in these patients DIC was initiated; however, the authors did not do bone marrows in the thrombocytopenic patients to rule out decreased platelet production, or thrombin times, reptilase times or 3P tests, all of which are necessary to fully delineate the existence of DIC. The authors did repeat heparin infusions in two patients who had developed thrombocytopenia on the earlier heparin therapy and were able to reproduce the thrombocytopenia.

#### *Extracorporeal Circulation*

Another clinical situation frequently leading to thrombocytopenia is that of extracorporeal circulation, especially during cardiopulmonary bypass. Umlas /38/ studied platelet counts and template bleeding times (as described by Mielke et al /39/) in a group of 22 patients prior to undergoing bypass and at three and 20 hours postbypass. The patients were divided into two groups according to the type of transfusion therapy they were given during surgery. Group A consisted of 11 patients who received only frozen RBCs which contained no platelets, and Group B consisted of 11 patients who were given one to four day-old bank blood which contained some viable and functional platelets, with or without additional FFP and frozen RBCs. Table 8 shows that three of the 11 Group A patients developed platelet counts of less than  $100,000/\text{mm}^3$  at three to 20 hours postbypass ( $64,000/\text{mm}^3$  to  $91,000/\text{mm}^3$ ), but that all three patients had bleeding times that were shorter than predicted from their platelet counts and, in fact, all had normal bleeding times. Harker and Slichter /40/ have shown a linear relationship between the template bleeding time and the degree of thrombocytopenia below  $100,000/\text{mm}^3$  in patients with thrombocytopenia because of a production defect (Fig. 10). In Group B (Table 9), seven of the 11 patients showed a nadir platelet count of less than  $100,000/\text{mm}^3$  (ranging from  $50,000/\text{mm}^3$  to  $90,000/\text{mm}^3$ ) three hours after the bypass, and six of the seven also had prolonged bleeding times. However, in five of these seven cases the bleeding time, though prolonged, was actually shorter than predicted from their platelet counts, and two of the seven had bleeding times that were more prolonged than predicted; at 20 hours postbypass,

TABLE 8  
PATIENTS RECEIVING ONLY FROZEN ERYTHROCYTE TRANSFUSIONS

Patient	Operation	Prebypass		3 Hours Postbypass		20 Hours Postoperative		Transfusion		Perfusion Time (min.)
		Plt. Ct.	TBT (min.)	Plt. Ct.	TBT	Plt. Ct.	TBT	O.R.	1st 24 Hours	
AC	ASD	266	2	134	7			3	2	34
ME	CBG	389	4	174	7	200	5	3	2	34
HA	MVR	221	3	115	5.5	147	4.5	4	2	100
TSS	AVR	225	3	64	4 (13.9) †	90	6 (6.6) †	8	1	117
EM	MVR	250	4.5	128	3	125	4.5	1	3	97
JM	BCBG	430	3	135	1	180	2.5	7	3	115
SY	CABG	188	3	91	5 (6.9) †	93	4.5 (6.3) †	4	3	72
PC	MVR	238	6.5	70	6 (12.3) †	61	6 (14.7) †	2	5	114
	TVP									
MJ	BCBG	255	4	135	4.5	165	3.5	3	6	75
RM	BCBG	466	3	136	6	136	6.5	8	2	103
KM	CBG	358	6	237	6.5	210	4.5	2	2	75
Mean ‡		299	3.8	129	5.5	140.7	4.8	4.1	2.8	85.1
		±94.7	±1.4	±50.5	±1.8	±49.4	±1.2	±2.5	±1.5	±30

Abbreviations: Plt. Ct. = platelet count ( $\times 10^3/\text{cu mm}$ ); TBT = template bleeding time

\* From Umlas J: In vivo platelet function following cardiopulmonary bypass. *Transfusion* 15:

596-599, 1975. Reprinted with permission from the author and the publisher, J.B. Lippincott Co.

† Measured TBT faster than predicted TBT (in parenthesis) for platelet count below 100,000/cu mm.

‡  $\pm 1$  SD

TABLE 9  
PATIENTS RECEIVING SHELF BLOOD WITH OR WITHOUT  
FROZEN ERYTHROCYTES AND FRESH FROZEN PLASMA\*

Patients	Operation	Prebypass		3 Hours Postbypass		20 Hours Postoperative		Transfusion		Perfusion Time (min.)
		Plt. Ct.	TBT (min.)	Plt. Ct.	TBT	Plt. Ct.	TBT	O.R.	1st 24 Hours	
WH	BCBG	371	2.5	90	6 (6.6) †	55	10.5 (16.2)	10	1	191
ES	MVR	236	3	116	6	108	6	8	2	96
J Mit	TCBG	384		70	9.5 (12.3)*	51	8.5 (17.3) †	9	3	183
JR	AVR	334	3	89	9 (7.4) ‡	163	4.5	11	1	168
	GBG									
JB	CBG	309	4	75	7.5 (11) ‡	92	4.5 (6.6) †	5	3	106
RD †	MVP	178	3.5	77	10.5 (12.5) †			9	2	108
J Mit †	MVR	170	5	50	16 (17.5) †	76	6 (10.8) †	6	3	95
AD	VA	351	2.5	199	3	175	3	4	2	78
	CBG									
MA	VA	232	4.5	130	3	139	6	4	1	49
MB	MVP	229	2	113	4.5			2	8	113
MV ‡	MVR	294	6	88	13 (7.7) ‡	123	7	7	1	103
Mean §		280.7	3.6	99.7	8	109.1	6.2	6.8	2.5	117.3
		±75.8	±1.3	±40.1	±4.1	±44.8	±2.3	±2.9	±2	±44.6

\* From Umlas J: In vivo platelet function following cardiopulmonary bypass. *Transfusion* 15:

596-599, 1975. Reprinted with permission from the author and the publisher, J.B. Lippincott Co.

† Measured TBT faster than predicted TBT (in parenthesis) for platelet count below 100,000/cu mm.

‡ Measured TBT longer than predicted TBT (in parenthesis) for platelet count below 100,000/cu mm.

§  $\pm 1$  SD



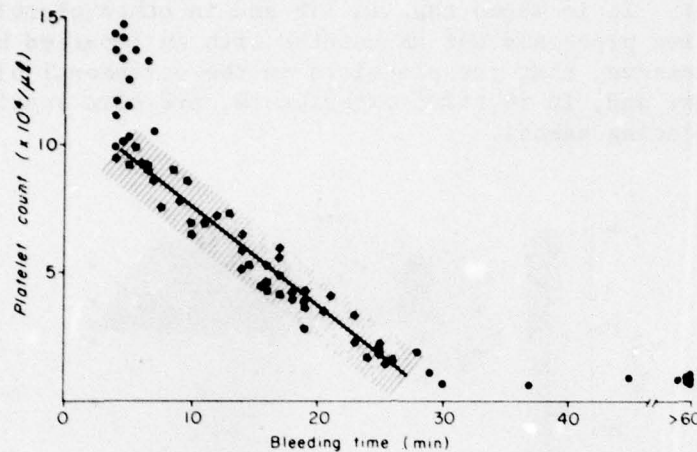


Figure 10. Inverse relation of bleeding time to circulating platelet count in patients with thrombocytopenia on the basis of impaired production when the concentration of platelets is between 10,000 and 100,000 per microliter. The regression line is shown by the solid line, and 95% confidence limits are indicated by the shaded area. From Harker LA, Slichter SJ: The bleeding time as a screening test for evaluating platelet function. *N Engl J Med* 287:155-159, 1972. Reprinted with permission from the authors and the publisher, New England Journal of Medicine.

four patients still had low platelet counts (51,000/mm<sup>3</sup> to 92,000/mm<sup>3</sup>) but only two of the four had abnormal bleeding times, and in both instances it was shorter than predicted. In only one patient was the bleeding time longer at 20 hours than at three hours postbypass. The group getting only frozen RBCs needed no more transfusions during surgery or in the postoperative period than the group receiving blood containing platelets. The mean platelet counts in the two groups were 130,000/mm<sup>3</sup> for Group A, and 99,000/mm<sup>3</sup> for Group B. The platelet counts did not correlate with the degree of abnormality of the template bleeding times. Thus in this study, though thrombocytopenia was common, it did not apparently often lead to a functional impairment of hemostasis. This may be explained by the fact that the thrombocytopenia led to the release of younger, larger platelets which appear to be more hemostatically competent. This fact was shown by Harker and Slichter /40/ in their group of 12 patients with ITP, all of whom had normal to slightly prolonged bleeding times (6.9±2.6 minutes) despite platelet counts of 17,000±10,000/mm<sup>3</sup>.

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PRESENT CONCEPTS IN INTERNAL MEDICINE HEMATOLOGY-ONCOLOGY SYMPO--ETC(U)

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(Fig. 11). It is known that in ITP and in other platelet consumptive processes not associated with an impaired bone marrow reserve, that the platelets in the peripheral blood are larger and, in *in vitro* experiments, are more sensitive to aggregating agents.

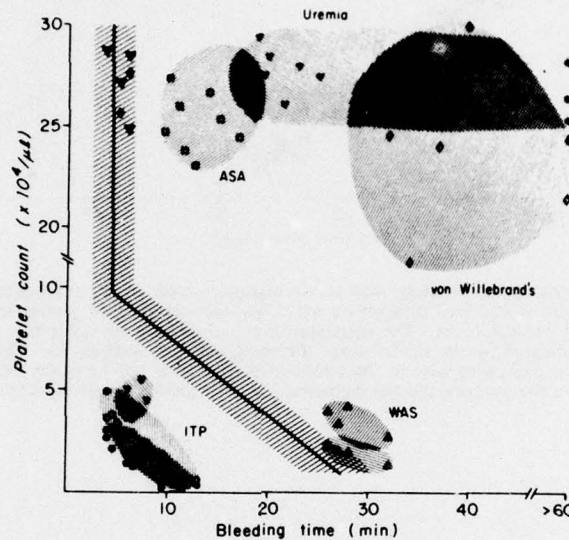


Figure 11. More than predictable shortening of the bleeding time for normal platelets by young platelets, as found in patients with idiopathic thrombocytopenic purpura (ITP) (●) or rapidly returning bone-marrow function after chemotherapy (▼). Bleeding times remain short even after adjustment for the increase in platelet volume (○). Impaired platelet plug formation is reflected as bleeding times longer than predicted by the platelet count as shown by 3 g of ASA daily (□) and von Willebrand's disease (◇), which corrects with cryoprecipitate infusion (◆). In uremia platelets have marked dysfunction in the untreated state (▼), which improves after hemodialysis (▽) and reverses to normal with peritoneal dialysis (▽). The modestly disparate bleeding times in Wiscott-Aldrich syndrome (WAS) (▲) become appropriate after adjustment for the small platelet volume (△). From Harker LA, Slichter SJ: The bleeding time as a screening test for evaluating platelet function. *N Engl J Med* 287:155-159, 1972. Reprinted with permission from the authors and the publisher, New England Journal of Medicine.



In another study, Umlas /41/ examined the role of DIC and fibrinolysis in open heart surgery patients as an explanation for their hemostatic abnormalities. No blood was used to prime the pump. The patients were examined preoperatively for the presence of FDPs (titers of less than or equal to 1:8 were considered normal), and repeat determinations were done at three and 20 hours postoperatively on both serum and chest tube drainage specimens. Platelet counts, PTT, PT, and blood fibrinogen levels were also done preoperatively one-half hour after the start of bypass and at three and 20 hours postoperatively. Twelve patients received only frozen RBCs, and another 16 were given bank blood, FFP, and platelets "as needed." In comparing the two groups, he found no significant differences in the level of FDPs in the blood and chest tube drainage, the blood fibrinogen levels, or in the change in platelet counts. The serum FDPs increased only twofold from the preoperative values to three hours postoperatively, but the chest tube FDPs had increased tenfold at that point. The level of chest tube FDPs did not correlate with the blood fibrinogen level, the amount of chest tube drainage, or the transfusion requirement. The blood fibrinogen and platelet levels dropped as early as one-half hour after bypass was begun, with only a small additional drop throughout surgery. Three hours postoperatively the fibrinogen levels had already risen (in the 21 patients in whom it was measured) from the immediate postoperative value in 11 of the 12 patients who were given only fibrinogen-free frozen RBCs. Thus, the study showed no evidence that DIC played a significant role in this situation. The disparity between serum and chest tube FDPs indicates that fibrinolysis was occurring in the chest tube drainage, and that these FDPs did not significantly reenter the circulation. The drop in platelets was felt to represent dilution, sequestration, or deposition on the pump membrane.

Other authors /42/ have noted similar changes in the platelet count in bypass surgery. Parker-Williams /43/ in a review on the subject of platelets from pumps noted that the drop in platelet count averages about 50% from preoperative values and begins immediately after beginning of pump bypass, reaching a nadir at about one hour of pump time and showing little further drop with longer pump times. Hypothermia exacerbates the thrombocytopenia. The platelet count continues to drop, reaching a nadir by the second or

third postoperative day, but returns to preoperative values by day eight; this is followed by a thrombocytosis equaling 130% to 180% of the preoperative levels. This drop is unrelated to the age of the stored blood or to the anticoagulant used in the blood (acid citrate dextrose or heparin).

Woods et al /44/ removed platelets from fresh whole blood, gave the blood during the bypass procedure, and the platelets were administered after the procedure, following neutralization of the heparin with protamine. Patients so treated were found to have higher platelet counts postoperatively than did those who did not have this type of transfusion procedure; they also had less bleeding. The role of platelet transfusions in postpump patients is further clouded by the fact that the degree of thrombocytopenia is related to the type of pump oxygenator used, i.e., smallest in the Temptrol and the disc oxygenator and highest in the Rygg and the Travenol 6LF oxygenator. /45/

Platelet loss ranging from 0% to 40% is also seen during hemodialysis and is less marked with the Kiil dialyzer than with the coil. /46/ As with cardiopulmonary bypass pumps, most of this loss occurs shortly after the onset of dialysis. Platelet deposition on the membrane occurs in spite of adequate heparinization. Although bleeding from this is uncommon, the membrane efficiency is impaired.

#### Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are probably similar diseases, presenting in different age groups; HUS occurs in childhood and has a better prognosis than the TTP of adults. Both disorders should be considered syndromes, as their etiologies are completely unknown and they can probably be set off by multiple stimuli, primarily viral infections. Over 300 cases of TTP have been described since 1925. Clinically, TTP presents as a pentad of findings:

- Thrombocytopenia - manifested by petechiae, ecchymoses, and purpura in about 60% of cases, with gross hematuria in 18%, retinal hemorrhages in about 20%, and epistaxis in 12%



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- Neurologic manifestations - these occur in 90% of patients and are manifested by headaches, mentation changes, paresis, and coma
- Fever - occurs in virtually 100% of cases and in about 20% is marked (39.4 to 40.0 C)
- Renal manifestations - occur in about 90% of patients as hematuria, proteinuria, casts, azotemia, and renal shutdown
- Microangiopathic hemolytic anemia

Amorosi and Ultman /47/ in a retrospective study of 271 patients listed the most common complaints on presentation: neurologic disorders - 60%; purpura or hemorrhage - 44%; malaise, fatigue, and weakness - 25%; nausea and vomiting - 24%; fever - 20%; pallor - 17%; abdominal pain - 11%; jaundice - 9%; arthralgia/myalgia - 7%.

The laboratory values were as follows:

- Anemia in 96%, ranging from 5.5 to 10.5 gms% in 174 of the 240 patients in whom it was listed
- Reticulocytosis in 19%, with a range of 3% to 80% in 90% of the patients
- Hyperbilirubinemia in 88%; almost always indirect
- Leukocytosis in 145 of the 239 patients in whom it was listed, often with a left shift toward immature forms
- Thrombocytopenia in 216 of the 224 patients in whom it was listed, ranging from 10,000/mm<sup>3</sup> to 120,000/mm<sup>3</sup>.

Lerner et al /48/ believe that there should be no coagulation abnormalities in this syndrome lest it be confused with DIC. In fact, DIC and TTP may be thought of as a continuum of pathophysiology, the symptoms and signs appearing different only at the extremes of hemostatic derangement. Jaffe et al /49/ examined various parameters of



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TABLE 10  
COAGULATION DATA\*

Patient No	Hospital Day	PT (sec)	PTT (sec) P/C	TT (sec) P/C	FIB (mg/100 ml)	V (%)	VII-X (%)	VIII (%)	FRA ( $\mu$ g/ml)†	F <sub>1</sub> Test‡	Hgburia§
1	1	12.6	30/33	27/24	185	92	120			0	0
	3				210						0
	7	12.5	34/37		310						0
2	2	10.2	34/34	22/27	410					0	0
3	3	12.6	34/41		230	110				0	0
	8	11.6	37/42		194						0
4	4	12.9									
5	5	12.2	37/36	25/25	292	90	155	140		0	0
	16	16.8	106/37	58/21	292	130	80				++
	23	14.3		55/25	158	90	60				
	25			40/28	98						
	26				129						
	28		35/38	34/25		100	59				
	29	13.0	44/38	31/20	292	70	92				
6	1	12.1	30/38		240	78	100+	52			0
	1	12.6	32/30		364	66	80			1:32	++
7	3	14.8	29/27								+
	4	14.2	29/31	22/20	220	110	60			0	
	6	13.1	28/29	28/20	190	88	50				
	7	12.5			247						
8	10	12.4	31/29	27/18							+
	1	11.8	50/45		358	95	100	100	24		+
	2		48/45		286	52	85	85	32		++
	3	17.0	57/45	20/10	234	62	98	98	32		+++
	4	19.9	90/45	32/10		60	48	48	32		+++
9	5	23.6	64/45	93/10	312	52	45	45	32		+++
	1	12.2	45/44	15/11	527	45	100	65			+++
	5	13.4		13/10	540						
10	1	12.2	36/42	15/11	624	85	41	100+	8		
	7	14.0	33/39	18/11	360	85	41	100+	8		++
	10	12.0	49/41	11/11	456				9		
	12	16.0	40/40	16/11	320	64		200	52		
11	1	12.3	42/32	12/10	372						++
	2	12.6	33/40	12/10	453	140	110				+
12	2	13.0	36/42	14/10	125	74	86				+++
	3	11.7	35/43	14/10	181	82	80	130			++
	4	13.2	32/40	12/10	204	92	100				+
	5	14.0	32/42	11/10	244	125	105	175			+

Abbreviations: PT = prothrombin time; P/C = patient/control; PTT = partial thromboplastin time; TT = thrombin time; FIB = fibrinogen; Roman numerals = clotting factors; FRA = fibrinogen-fibrin-related antigen.

\* From Jaffe EA, Nachman RL, Merskey C: Thrombotic thrombocytopenic purpura - coagulation parameters in 12 patients. *Blood* 42:499-507, 1973. Reprinted with permission from the authors and the publisher, Grune & Stratton, Inc.

† Normal < 4  $\mu$ g/ml

‡ Normal titer  $\leq$  1:2

§ Hemoglobinuria-rated 0 to 3+ on basis of severity

Present Concepts, Hematology-Oncology Symposium, Winter 1977-1978

coagulation in a series of 12 patients who clinically met the criteria for TTP (Table 10) and found that coagulation abnormalities were uncommon:

- The plasma fibrinogen was less than 150 mg% in only two patients.
- The PT was prolonged in four patients.
- The PTT was prolonged in two patients.
- The TT was frequently prolonged (in eight of 10 patients).
- Factor V levels were less than 50% of normal in only one of 11 patients.
- Factor VIII levels were less than 50% of normal in one of six patients.

Harker and Slichter /50/ measured platelet survival and fibrinogen survival in four patients with TTP and found that all four had shortened platelet survival, but that none had an abnormal fibrinogen survival. These data imply that TTP and DIC do indeed have different pathophysiological consequences.

In TTP there is deposition of a hyaline-like material in the vessel walls with a concomitant endothelial proliferation. This hyaline material stains for fibrin, and platelets have also been found in it. Such lesions are not unique to TTP; they are also seen in DIC. The arteriolar and capillary deposition of fibrin strands serves to "clothesline" the RBCs as they pass by, thereby yielding the characteristic schistocytes. The vascular damage leads to the renal shutdown and the central nervous system effects, as well as infarction of other tissues, including heart, adrenal glands, pancreas, lymph nodes, spleen, and the gastrointestinal tract.

Thrombotic thrombocytopenic purpura is lethal in about 90% of cases within three months of onset. In some cases, it is self-limited and reversible, and occasionally seems to lead to a chronic variety. Thrombotic thrombocytopenic purpura

has been described in four of seven siblings in the same family over a period of 10 years; one sibling recovered and one had repeated episodes over a period of several years before he finally died of the disorder. /51/

Therapy has not been proven to be beneficial in changing the morbidity or mortality of the disorder. The touted results of a wide variety of agents including splenectomy, heparin, dextran, aspirin, persantin, steroids, and various combinations of these, are based on one or two case reports without rigorous exclusion of DIC as the etiology of the disorder treated. No one study has a large enough series in which patients were well studied and consistently treated, much less with a concurrently followed control group. Certainly, the role of splenectomy can be questioned on the basis of a case of TTP that developed in a 26-year-old man who underwent splenectomy three months prior to onset of the disorder. /52/ Most survivors have been treated with steroids, splenectomy, and antiplatelet drugs.

#### DECREASED PLATELET PRODUCTION

##### A. By Depression of Megakaryocytes by Drugs

*Hydrochlorothiazide* - A mild decrease in platelets may occur in up to 25% of patients who take this drug. The onset of the thrombocytopenia is slow. Recovery after discontinuation of the drug often takes one to two months.

*Ethanol* - This drug has a direct toxic effect on the megakaryocytes, similar to its effect on the myeloid and the erythroid marrow elements.

*Corticosteroids* - High doses of this drug have resulted in suppression of megakaryocytes, but a dose-response curve is not available.

*Estrogens* - There is weak evidence for suppression of platelet production by these agents.

*Tolbutamide*



**B. Ineffective Thrombopoiesis**

- Paroxysmal nocturnal hemoglobinuria (PNH)
- Megaloblastic anemias - in pernicious anemia, the thrombocytopenia is usually mild to moderate.
- DiGuglielmo syndrome (erythroleukemia) appears to involve all cell lines or some common stem cell.

**C. Hypoplastic and Aplastic Anemias**

The following agents regularly cause these anemias when given in adequate doses:

- Benzene
- Radiation
- Alkylating agents such as Cytosan<sup>®</sup>, nitrogen mustards, busulfan, melphalan, chlorambucil, thiotepa, and the nitrosoureas, another class of chemotherapeutic agents which seem to act by similar mechanisms
- Antimetabolite drugs - ARA-C, 6-TG, 6MP, 5FU, hydroxyurea
- Antitumor antibiotics - adriamycin, daunomycin, actinomycin D, and mitomycin C

The following agents are only occasionally associated with bone hypoplasia or aplasia:

- Antibiotics - chloramphenicol, quinacrine hydrochloride, organic arsenicals
- Anticonvulsants - Mesantoin<sup>®</sup>, Tridione<sup>®</sup>
- Analgesics - phenylbutazone, Tegretol<sup>®</sup>, Indocin<sup>®</sup>, and aspirin

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- Gold salts
- Antithyroid drugs - chlorpropamide and tolbutamide have been rarely reported to cause hypoplastic or aplastic anemia.
- Antihistamines
- Sedatives and tranquilizers are rare causes of aplastic/hypoplastic bone marrows.

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## Appendix

### CHEMICAL- INDUCED THROMBOCYTOPENIA

#### A. Agents that suppress platelet production:

##### 1. By generalized bone marrow suppression

a. Agents that are regularly associated with aplastic or hypoplastic anemia if given in sufficient doses:

(1) Benzene

(2) Ionizing radiation

(3) Alkylating agents - cytoxan,  $\text{HN}_2$ , busulfan, melphalan, chlorambucil (nitrosureas)

(4) Antitumor antibiotics - adriamycin, daunomycin, actinomycin-D, mitomycin-C

(5) Antimetabolites - ARA-C, 6-TG, 6-MP

b. Agents that are occasionally associated with marrow hypoplasia or aplasia:

(1) Antibiotics - the most commonly reported cases are with chloramphenicol, organic arsenicals, and quinacrine.

(2) Anticonvulsants - Mesantoin®, Tridione®

(3) Analgesics - phenylbutazone is the most common offender; also associated are Tegretol®, Indocin®, and aspirin.

(4) Gold salts

(5) Antithyroid drugs - these are rare causes (chlorpropamide, tolbutamide)

(6) Antihistamines - rare reports of Pyribenzamine

(7) Sedatives and tranquilizers - rare causes

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2. By selective suppression of the megakaryocytes

(1) Chlorothiazides

(2) Ethanol

(3) Tolbutamide

(4) Estrogens

B. Agents that lead to the production of antiplatelet antibodies:

(1) Sedormid

(2) Chlorothiazide

(3) Digitoxin

(4) Dilantin

(5) Gold salts

(6) Aldomet

(7) Para-aminosalicylic acid (PAS)

(8) Quinine and quinidine

(9) Rifampin

(10) Hydroxychloroquine

(11) Tegretol

(12) Sulfathiazole

C. Miscellaneous: There are over 65 agents that are associated with thrombocytopenia, but the mechanism is still unknown.

Pope has said that the "proper study of mankind is man" and even though a clinician has science, art, and craftsmanship, unless he is intensely interested in human beings he is not likely to be a good doctor.

— *Longcope*

The art of medicine has no constant rule.

— *Celsus*

Blood transfusions are a most dangerous form of Russian roulette: the pathologist loads the gun, the clinician pulls the trigger but the gun is held to the patient's head.

— *Anonymous*

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